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A Journal of Neurology

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PART 1, VOL. 58.

STUDIES IN THE NEUROLOGICAL MECHANISM OF PARATHYROID TETANY.

BY RANYARD WEST,
Beit Memorial Research Fellow.

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INTRODUCTION.

THE paper which follows is a contribution in a certain limited field in the wide problem of the mechanism by which the muscular spasms of tetany are produced.

In recent years the study and the literature of tetany have been considerable. As a condition it is not easy to define, of its essential nature we are ignorant. Its predominant manifestation is of muscular contractions of widespread regional distribution and of divergent forms. In man and in certain higher mammals distinctive postures occur. A variety of changes in the chemical composition of the blood are associated with tetany; the condition has been nevertheless recorded in the absence of such changes. Tetany has been found associated with a number of diseases of the central nervous system, though it also occurs in the absence of any demonstrable disease of the brain, spinal cord or peripheral nerves.

It is profitable to study the mechanism of the production of muscle contractions in a specific form of tetany, that arising from parathyroid extirpation. Only the neuro-muscular mechanism involved is considered, and this only in certain of its aspects. Similar studies have been made before [1, 2, 3, 4] but the views of the problem as a whole differ somewhat from the one taken here, and not in all cases have my observations and deductions coincided with those of previous writers. Certain phenomena are newly recorded.

PART I.

THE MODIFICATION OF PARATHYROID TETANY BY PERIPHERAL NERVE SECTION.

Partial or complete denervation of one hind limb was undertaken in seven dogs. In four, the sciatic nerve was divided in the gluteal region; in the remaining three the combined anterior and posterior roots of segments 3, 4, 5, 6, 7, 8 in the lumbar region of the spinal cord were cut. The operation was done on the left side, extra-thecally, and the cauda equina was transected immediately below the last severed root. Tetany was induced by parathyroidectomy. Eleven observations were made at intervals varying from four and a half hours to twenty days after nerve section.

Parathyroid tetany in dogs may be classified in its motor manifestations as :—

(1) *Tonic tetany*, where continued contraction of a muscle or a group of muscles produces a strongly marked posture.

(2) *Clonic tetany*, where whole muscles, or a large proportion of the fibres of a muscle, contract synchronously or nearly synchronously, producing a violent jerked movement of the limb, or a sharp twitch of an individual muscle. The clonic contractions of tetany frequently occur in a flaccid limb; they are variable and irregular in frequency, but may reach a rate and occasion grouping suggesting the beating of a kettle-drum. The latter form occurs characteristically in the scalp.

(3) *Fibrillary tetany*, consisting of a rapid repeated contraction of a small group of fibres in one or more areas, not infrequently scattered widely throughout the musculature of the body.

It has been stated by Paton, Findlay and Watson [1] that section of the nerves to any part entirely and immediately abolishes all spasms, tremors and jerkings of the muscles supplied. My observations suggest that, in the case of the dog, if twenty-four hours are allowed to elapse between the nerve section and the onset of tetany, the latter will seldom be seen in the denervated muscles (*see* Table I), but fibrillary tetany can undoubtedly occur in the first few hours after denervation, and in early stages grouped contractions large enough to be classed as "clonic" have been seen. The tonic (postural) element has, however, not been present in this series. In all cases where comparison was possible, the activity of the tetany was less in the denervated muscles than in the normal opposite limb.

Clonic tetany was clearly seen in the case of tetany precipitated four and a quarter hours after nerve section, and in no other case. (Table I, Dog 1.) In the one case marked "Doubtful Result" (Dog 7, third day), tetany was probably absent, but it was not certain that the limb was flaccid throughout. In all the remaining cases fibrillary tetany was either continuously present or never observed.

Table I shows the time after denervation at which tetany was induced, the presence or absence of tetany in the denervated muscles, and the condition of the opposite hind limb.

TABLE I.

Dog	Site of section	Time after section	Tetany and denervated muscles	Tetany in opposite hind limbs
1.	Sciatic	4¼ hours	Chronic and fibrillary tetany in flexors and extensors below knee	Tonic extension, clonic and fibrillary
2.	Spinal roots	5 hours 6 hours	Fibrillary tetany throughout	Fibrillary and slight tonic
3.	Spinal roots	7 hours	Fibrillary tetany in hamstrings, gastrocnemius	Some tonic extensor. Fibrillary active
4.	Sciatic	12 hours	No tetany	(Both sides denervated)
5.	Sciatic	24 hours	Fibrillary tetany in hamstrings	(No observations)
6.	Spinal roots	2 days	No tetany	Tonic, fibrillary, occasional clonic
7.	Sciatic	3 days	Doubtful result	(Both sides denervated)
8.	Spinal roots	3 days	No tetany	Some tonic extensor. Fibrillary active
6.	Spinal roots	4 days	No tetany	Fibrillary
6.	Spinal roots	5 days	No tetany	Tonic, clonic and fibrillary
4.	Sciatic	13 days	No tetany	Tonic and clonic
7.	Sciatic	20 days	No tetany	(Both sides denervated)

Electrical reactions in denervated tetany preparations.—Electrical reactions obtained by a stimulating electrode placed on the skin [7] have been recorded in tetany in dogs [8]. In denervate preparations, apart from tetany, certain anomalous electrical reactions were obtained and are recorded elsewhere [9]. Briefly, a phase of hyperexcitability occurs on about the fifth day after denervation and persists as long as it has been studied (to the twentieth day). This effect, on the eighth day, is shown in Table II. Table III shows the reactions in the same dog in tetany. It will be seen that while the notable fall of threshold, especially and characteristically, of the kathodal opening current (K.O.C.), has occurred on the normal side, the denervated side has not fallen further. The reading in tetany on the denervated side was higher in each item than it had been since the fifth day of denervation. In this case tetany was precipitated on the twenty-second day. No tetany occurred in the denervated limb.

TABLE II. (BEFORE PARATHYROIDECTOMY.)

Stimulus	Left (denervated, 8th day)	Right (intact limb)
K.C.C.	0·1 milliampere	1·8 ma.
K.O.C.	0·25 ,,	6·0 ,,
A.C.C.	0·15 ,,	2·3 ,,
A.O.C.	0·25 ,,	8·5 ,,

TABLE III. (IN TETANY—22ND DAY.)

Stimulus	Denervated		Intact limb
	Occasion 1	Occasion 2	
K.C.C.	0·5 ma.	0·7 ma.	0·4 ma.
K.O.C.	0·45 ,,	0·2 ,,	0·4 ,,
A.C.C.	0·6 ,,	0·18 ,,	0·8 ,,
	1·0 ,,	0·5 ,,	0·5 ,,

If, however, tetany be induced on the second day after section, and thus before the electrical effects of denervation are apparent, the characteristic fall in threshold occurs. (Table IV.)

TABLE IV. (2ND DAY.)

	Limits of five previous readings	In tetany
K.C.C.	0·5 to 0.8 ma.	0·5 ma.
K.O.C.	5·0 to 10·0 ,,	0·5 ,,
A.C.C.	1·6 to 2·3 ,,	0·2 ,,
A.O.C.	1·9 to 3 5 ,,	0·5 ,,

It was doubtful whether slight tetany was present in the denervated limb or not.

Another case was seen in both phases. The left radial and ulnar nerves had been severed. On the second day latent tetany was doubtful, by the criterion of the hind-limb kathodal opening current threshold (1·5 ma.). The reactions in the fore-limbs, however, showed a fall which has never been found on the denervated side on the second day in the absence of tetany.

TABLE V. (2ND DAY.)

	Left (denervated)	Right
K.C.C.	0·5 ma.	0·29 ma.
K.O.C.	0·15 ,,	1·2 ,,
A.C.C.	0·3 ,,	0·75 ,,
A.O.C.	0·22 ,,	0·45 ,,

It will be noted that the K.O.C., in particular, is lower in the denervated limb than in the limb simply affected by tetany.

On the fourth day, the normal fore-limb and hind-limb showed fully developed tetany reactions. On the ninth and twelfth days latent tetany was still present, the readings for the latter day being :—

TABLE VI. (12TH DAY.)

	Left (denervated)	Right	Hind-limb
K.C.C.	0·1 ma.	0·4 ma.	
K.O.C.	0·3 ,,	0·45 ,,	0·5 ma.
A.C.C.	0·2 ,,	0·9 ,,	
A.O.C.	0·2 ,,	0·7 ,,	

Here the readings of K.O.C. are lowered on each side to a level characteristic of tetany.

On the fourteenth day, however, though tetany was still present, the reactions in the fore-limbs showed a rise in threshold on the denervated side.

TABLE VII. (14TH DAY.)

	Left (denervated)	Right
K.C.C.	0·98 ma.	0·2 ma.
K.O.C.	1·0 ,,	0·29 ,,
A.C.C.	1·3 ,,	0·85 ,,
A.O.C.	1·8 ,,	0·21 ,,

In a further case, in which tetany developed only four and a quarter hours after sciatic section, not only did hyperexcitability occur on the denervated side, but the K.O.C. was peculiarly low (0·075 to 0·09). In this case clonic and fibrillary tetany were definitely present on the denervated side, though less active than on the normal side.

These results suggest an exaggeration of the electrical hyperexcitability of tetany in the early stages (first few hours) of degeneration of a peripheral nerve. After the phase of degenerative hyperexcitability has set in, however, no further fall of threshold occurs with the onset of tetany, the threshold even tending to rise on this event. These findings are summarized in Table VIII.

TABLE VIII.

Dog	Time after section	K.O.C. before tetany	K.O.C. in tetany	Rise or fall	Presence of tetany locally
1.	4¼ hours	1·75 ma.	0·09 ma.*	Fall (exag.)	Yes
6.	2nd day	5·0 to 10·0 ma.	0·5 ,,	Fall	?
3.	3rd day	2·0 to 4·4 ,,	0·25 ,,	Fall	—
3.	17th day	0·3 to 0·8 ,, †	0·9 ,,	Slight rise	No
6.	22nd day	0·075 to 0·25 ,, †	0·45 ,,	Rise	No

* Later 0·075, the opposite intact side being 0·25.

† Since onset of hyperexcitability on 5th day.

The progress of the changes from the 2nd to the 14th days can be followed in one animal :—

TABLE IX.

Day after denervation	K.O.C. normal side	K.O.C. denervated side	Tetany	Criterions of tetany
2nd	1·2 ma.	0·15 ma.	Not definite	Hind leg K.O.C. 1·5 ma.
9th	—	0·1 ,,	Not definite	—
12th	1·5 ,,	0·2 ,,	Latent	Hind leg K.O.C. 0·5 ma.
14th	0·29 ,,	1.0 ,,	Latent	Hind leg K.O.C. 0·32 ma.

Summary and Conclusions.

(1) Peripheral nerve sections were undertaken in seven dogs, and parathyroid tetany induced. Observations both upon the incidence of tetany and upon the electrical reactions were made.

(2) Clonic and fibrillary tetany can occur in muscles denervated a few hours previously (four and a quarter hours in these experiments).

(3) Fibrillary tetany can occur for at least twenty-four hours after denervation.

(4) Tonic tetany has not been observed after denervation.

(5) After the third day following denervation no elements of tetany have been detected. Observations have been continued as far as the twentieth day.

(6) The hyperexcitability to electrical stimuli which occurs in tetany is present to an exaggerated degree for some hours after denervation (forty-eight hours in the experiments). A second phase is subsequently found in which the electrical reactions of denervated muscle do not fall, but rather tend to rise with the onset of tetany.

PART II.

TETANY IN "SPINAL" DOGS.

Complete transection of the spinal cord in the region of the eighth dorsal segment was performed on six dogs. A seventh was subjected to transection at the level of the first dorsal segment. Parathyroid tetany was induced at varying periods after transection. Eleven observations upon the effect of tetany on the regions posterior to the section were made at intervals varying from six hours to thirty-six days. In addition, the effects of tetany upon the properties of the spinal preparations were examined. These observations are summarized in Table X.

TABLE X.

Dog	Time after spinal section	Tetany in normal fore-limbs	Tetany in hind-limbs	"Spinal" reflexes
1.	6 hours	Fibrillary only	Tonic (extensor), clonic and fibrillary	+ +
2.	30 hours	Fibrillary and slight clonic	Absent	(T.R.)
3.	5 days	(1) Tonic, fibrillary, slight clonic	Absent.	+ +
		(2) Tonic and fibrillary	? Spontaneous clonic	+ +
4.	6 days	—	Fibrillary only	+
4.	7 days	Fibrillary and clonic	Fibrillary and clonic	+
2.	8 days	Fibrillary only	Absent	(T.R.)
4.	11 days	Clonic and fibrillary	Clonic, fibrillary, occasionally tonic	+
4.	13 days	Clonic	Clonic	+
5.	14 days	Tonic, clonic, fibrillary	Tonic, clonic, fibrillary	+
4.	18 days	Occasional clonic	Occasional clonic	+ + § 1
6.	36 days	Tonic, clonic, fibrillary	Tonic, clonic, fibrillary	+ + § 2

+ = Present.
+ + = Very active.
§ 1 = Added reflexes.
§ 2 = Added reflexes.
T.R. = "Spinal preparation" reflexes absent, but tendon reflexes present.

Analysis of Table.

(1) *Occurrence of Tetany.*—Tetany was absent on three observations only out of eleven. On one of these occasions tetany was doubtfully present on the same day. The negative results bear no constant time relationship to the transection of the spinal cord, occurring as they do at thirty hours, five days and eight days after section. Tetany was present at six hours, six days and seven days after section. Two of the negative observations were on the same dog (Dog 2), in which active tetany was poor, fibrillary and slight tonic tetany being present on the occasion of the first observation (thirty hours), and only fibrillary tetany on the second occasion (eight days). Unlike the other five animals of the series, this dog never developed the characteristic reflexes of the chronic spinal preparation, though the tendon reflexes were present from the first day after section. . Further, the general condition of this animal was poor throughout, and especially so on the eighth day. It may be said, therefore, that in this series of "spinal" dogs tetany was definitely present on eight occasions out of eleven, and that in two of the three exceptions more than one factor was present which might render the one dog concerned an unfavourable subject.

The remaining exception (Dog 3, fifth day) requires further consideration. Parathyroidectomy was performed on the fourth day after transection of the cord. On the fifth day the following notes were made:—

11.30 a.m.: Lower limbs in posture of semi-flexion, slight resistance to passive flexion. Knee-jerks and ankle-jerks present and equal. Deep pressure on pad of foot produces a strong flexion reflex with crossed extension. Passive flexion produces crossed extension. Anal reflex present. No reflex stepping.

Upper limbs: Bilateral extensor rigidity. Resistance to passive flexion, sometimes modified when the "clasp-knife" phenomenon is shown. Fibrillary twitches and occasional clonic tetany in fore-limbs and scalp.

3.15 to 4 p.m.: Continuous fibrillary tremors in both fore-limbs; none in hind-limbs. Fibrillary twitches in trunk, extending posteriorly to about as far as, but not further than half way down, the scar of the spinal operation. During the forty-five minutes of observation two rapid flexion movements occurred in the left hind-limb. At the first of these there were flies round the limb, at the second it appeared as if the flexors of the thigh had twitched spontaneously. Apart from this no spontaneous movements of any kind were seen in the lower limb during this period.

There was thus tonic, clonic and fibrillary tetany in the forepart of the body during the morning, and fibrillary tetany in the same areas continuously for forty-five minutes during the afternoon. On neither occasion was any element of tetany observed in the posterior portion of the animal, despite considerable activity of the "spinal preparation" reflexes.

The eight occasions (four dogs) on which tetany occurred in the areas below the spinal section may now be discussed.

Dog 1.—Parathyroidectomy had been performed two days before transection of the cord was undertaken. Six hours after transection the following was noted: Fibrillary tetany in the muscles of the left shoulder and fore-limb. In the left hind-limb, occasional bouts of definite clonic tetany occurred combined with strong extensor tone. Right hind-limb, occasional bouts of clonic tetany were seen. In this dog the "spinal preparation" reflexes, which are discussed fully later in this paper, were very active at this stage.

Dog 4.—Tetany occurred on the sixth, seventh, eleventh, thirteenth and eighteenth days after transection. In all instances it was present in the hind-limbs and there was apparently no significant difference between the severity in fore and hind limbs. "Spinal" reflexes varied in activity, but were always present.

Dog 5.—All three elements of tetany were present in the hind-limbs on the fourteenth day after transection. The "spinal" reflexes were poorly developed in this case.

Dog 6.—Tetany was precipitated on the thirty-sixth day after transection. It occurred in all its forms in the hind-limbs, but with less extensor rigidity than in the fore-limbs. "Spinal" reflexes were very active throughout in this case.

(2) *Nature of tetany in "spinal" dogs.*—Parathyroid tetany in its three forms, tonic, clonic and fibrillary, has been observed in "spinal" dogs at various periods after cord transection.

Tonic tetany has been observed six hours, fourteen days and thirty-six days after transection. On only two occasions was this form of tetany present in the fore-limbs and absent in the hind-limbs, and on one occasion this finding was reversed. The posture seemed to be almost invariably extensor, and there did not appear to be any essential difference between tonic tetany in neurologically normal dogs and in acute or chronic "spinal" dogs.

Clonic tetany has been seen six hours, seven days, eleven days, thirteen days, fourteen days and thirty-six days after spinal transection. On only one occasion was clonic tetany present in the fore-limbs and absent in the hind-limbs, and on one other occasion this finding was reversed. In Dogs 1, 4, 5 and 6 the clonic twitches which occurred closely resembled those of tetany in a normal dog. In Dog 4, however, "The clonic extensor-jerks are slower than in tetany in normal animals, the period of contraction being extended to about half a second." Myotatic irritability and considerable excitability of "spinal" reflexes were present at the time. The case is discussed fully at a later stage in this paper.

Fibrillary tetany differed in no visible manner from that occurring in areas possessing a normal nerve supply.

On the whole there was a tendency for each type of tetany to make itself manifest earlier in the normal fore-limbs than in the "spinal" hind-limbs. In one or two cases tetany was more active in the normal than in the abnormal limbs, but on the whole this distinction was by no means obvious. In Dog 6 (thirty-sixth day) tetany was more pronounced in the fore-limb, while in Dog 1 (six hours) it was more active in the hind-limb.

(3) *Spinal preparation reflexes in tetany.*—The presence and form of the various reflexes associated with the spinal mammalian preparations were studied in conjunction with the variations occurring when tetany supervenes. Only one dog (Dog 2) failed to develop any of the reflexes. The dog was kept for nine days after transection of the cord. Parathyroidectomy was performed on the day prior to the transection. Tetany occurred thirty-hours and eight days after the spinal operation. Twenty-six hours after section and just prior to the onset of tetany the knee-jerks were both very active. At the onset of tetany (thirty hours) and on subsequent days the hind-limbs remained flaccid, the knee-jerks

were present but not very active, and on no occasion were any added reflexes present. This dog did not develop tetany in the hind-limbs. The remaining dogs may be taken in order.

Dog 1.—No observations were made before the onset of tetany. At the onset of tetany (six hours) the knee-jerks were present and exaggerated. In addition: (1) squeezing the pad of the left foot produced extension—not flexion—of that leg, a violent rapid thrust; (2) squeezing the pad of the right foot produced characteristic homolateral flexion and crossed extension; (3) there was a strong extensor posture present on account of the tetany. It is interesting to record the presence of a well-marked crossed extensor reflex within six hours of transection of the cord.

Dog 3.—No observations were made before the onset of tetany. At the onset of tetany (five days), the knee-jerks were present and equal. The posture of the hind-limbs was one of semi-flexion. Slight resistance to passive flexion was encountered. Deep pressure on the pads of the feet produced a strong flexion reflex with crossed extension. The anal reflex was present. There was no tetany in the hind-limb at the time of making this record. The fore-limbs showed bilateral extensor rigidity, resistance to passive flexion being of the "clasp-knife" type. Fibrillary and clonic tetany were present.

Dog 4.—Before parathyroidectomy, on the third day of section, the knee-jerks were exaggerated on both sides. Signs of flexion and of crossed extension reflexes were present. Twenty-four hours after parathyroidectomy, in the presence of electrical hyperexcitability, but seven hours before the appearance of active tetany and on the sixth day of section, the knee-jerks and flexion and crossed extension reflexes were present, but not very active.

At the onset of active tetany knee-jerks very brisk, fibrillary tetany in right hind-limb. Seventh day after section knee-jerks exaggerated, limbs flaccid; flexion and crossed extension reflexes present, but not very active. Fibrillary tetany was present. Subsequently the activity of the tetany was enhanced by heat when apparently spontaneous movements of the following nature were observed: (*a*) Flexion and extension of the left ankle occurring two or three times. The movement appeared co-ordinated and it was slow and deliberate in nature, occupying about half a second. This was followed by (*b*) spontaneous bilateral extension of both hind-limbs upwards, against gravity, the dog being upon his back at the time. The left leg extended first, both resisted passive flexion and remained extended for some moments. At this time the fore-limbs were not rigid, only fibrillary tetany being present. Subsequently (*c*) flexion which appeared to be active occurred and both limbs remained flexed. Later on the same day these three phases were repeated, the right ankle now moving before the left. The knee-jerks were extremely active and the flexion reflex much more brisk than heretofore. Phillipson's reflex was active.

On the tenth day, when active tetany was not present, the flexion and crossed extension reflexes were obtained, but had lost a great deal of their activity. On the eleventh day, when tetany had again been enhanced by heat, spontaneous movements were again present, smooth extension against gravity being repeatedly observed. On the twelfth day an increase of the briskness of both flexion and crossed extension reflexes occurred without activation of tetany. On the thirteenth day active tetany spontaneously returned. It was clonic in form. The "spinal" reflexes were again very active; the crossed extension reflex varied from its usual form in that passive flexion of one leg led to repeated flexion and extension of the opposite leg.

Dog 5.—Before parathyroidectomy, on the third day after section, both knee-jerks were obtained, but no added reflexes and no spasticity were present. On the fifth day slight spasticity occurred and both flexion and crossed extension reflexes were obtained. On the sixth day the response to the flexion and the crossed extension reflexes was sluggish and prolonged. On the eleventh day flaccidity had occurred and the "spinal reflexes" were feeble. On the twelfth day both flexion and crossed extension reflexes were absent; the hind-limbs were flaccid and the knee-jerks not exaggerated. On this day parathyroidectomy was performed.

Two days after parathyroidectomy clonic tetany appeared in the scalp and fore-limbs. The knee-jerks had become brisk. Great myotatic irritability (to be referred to subsequently) occurred in the hind-limbs. The flexion and crossed extension reflexes returned though they were not active. Spontaneous micturition reflexes occurred, the two hind-legs flexing simultaneously, micturition occurring and bilateral extension of the hind legs following. A few hours subsequently spontaneous flexion and extension occurred in the hind legs, both legs being rigidly extended, then one flexing and remaining flexed. The crossed extension reflex was present but was distorted. Passive flexion of the right leg produced extension of the left leg while passive flexion of the left leg led repeatedly to flexion of the right leg.

Dog 6.—Before parathyroidectomy this dog was observed from the fifth to the thirty-fourth day. On the fifth day the knee-jerks were obtained and there was slight spasticity. The crossed extension reflexes were present and equal. On the seventh day spasticity had increased and this continued to increase subsequently. On the nineteenth day the knee-jerks were very brisk, the flexion reflex was present, but sometimes irregular, a rapid jerk to half-flexion being followed by a much slower completion of the movement. On the twentieth day, passive flexion of one leg was found sometimes to excite extension and sometimes flexion of the other. Pinching the toes of one leg excited flexion on that side, then opposite extension, followed by a reversal of the movements, a marching reflex. On occasion passive flexion of one leg excited a series of extensor thrusts on the opposite side, a crossed pawing reflex.

Parathyroidectomy was performed on the thirty-fourth day. A few hours prior to the onset of active tetany the distribution of tone in the hind legs enabled the dog to stand on all four legs for several seconds.

After the onset of tetany the following observations were made :—

(1) When the dog was held up spontaneous pawing and marching reflexes were constantly repeated, continuing actively for minutes at a time. The activity of these movements had never been approached before the onset of tetany.

(2) The dog "marched" and "pawed" even when lying on his side.

(3) The crossed extension and the flexion reflexes, elicited in the usual way, produced violent jerked movements, much more rapid and active than before tetany.

(4) *Electrical reactions in tetany in "spinal" dogs.*—Stimulation was with a small electrode applied to the skin over the muscles to be tested, a large indifferent electrode being applied to a distant part of the body. The circuit described elsewhere was used [7]. No significant alteration of threshold occurred in the hind-legs as a result of transection of the spinal cord; a tendency towards higher readings in the hind-limb is found under normal conditions. With the onset of tetany, at whatever period after transection this occurred, the electrical thresholds fell coincidently in the fore and hind limbs to the usual degree, the kathodal opening contraction being in the region of one-tenth its normal value.

(5) *Other observations on tetany in "spinal" dogs.*—In observing the phenomena of tetany in these six "spinal" dogs certain matters of interest, some confirmatory of previous observations, others seen for the first time, were recorded.

(*a*) *The effect of heat.*—A dog in latent tetany can frequently be thrown into active tetany by exposing it to heat just sufficient to cause panting [10]. Perhaps an added alkalosis is responsible for this. If fibrillary tetany is present before heating, well-marked clonic or tonic tetany can usually be induced within five minutes of the dog commencing to pant. Cooling the animal removes the symptoms coincidently with the cessation of panting. In one or two instances, inhalations of oxygen containing 10 per cent. of carbon dioxide relieved the tetany within a few minutes.

But in addition to the effect of heat upon the animal as a whole, radiant heat from an electric radiator exercised an effect upon the muscles irradiated. This effect appeared to be either peculiar to, or very much more pronounced in, the "spinal" hind-limbs, in contradistinction to the normally innervated fore-limbs.

Dog 4.—The dog was in fibrillary tetany. When a hind-limb was irradiated the muscles became very sensitive to touch. A light tap on a flexor of the knee would produce contraction locally, flexion of the knee and a movement of the tail. No such effect was present in the fore-limbs and it was also absent in the opposite hind-limb which was kept cool. This observation could be repeated alternately in the two hind legs by turning the dog over from side to side. Finally a touch would cause the whole limb to jerk and the tail to twitch, while the reflexes and the myotatic irritability were not changed in the front leg in response to similar treatment. The flexion reflexes were present, but not very active at this time.

(*b*) *Myotatic irritability in tetany.*—In addition to this myotatic irritability produced by heat, the muscles of a dog in tetany are hyperexcitable to mechanical stimuli, apart from heat. Very active fibrillary contractions occur on cutting such muscles with a knife. This had previously been noted in the case of the scalp muscles in decerebrating a dog in tetany. It was confirmed in the muscles of the "spinal" preparation.

(*c*) *Increased response of muscle to mechanical excitation of nerve.*—In one dog of the series (No. 4) the sciatic nerve on the left side was exposed during mild active tetany. It was found that digital manipulation of the nerve excited extensor twitches in the opposite leg and foot. No movement occurred on the side stimulated. The nerve was merely rolled under the finger, and each roll produced a definite rapid extension. The right sciatic was exposed, and a similar crossed reaction noted. The possible analogy between this observation and Chvostek's sign is interesting.

(*d*) "*Spontaneous*" *movements.*—These have been recorded above (Dogs 4, 5, 6). In all three cases the movements occurred at a time when the "spinal" reflexes were unduly brisk, and in Dog 6 movements were performed analogous to the "marching" or "pawing" reflex. The general nature of these movements and the associations mentioned above perhaps make it probable that they were in reality reflex movements set in motion by a small peripheral stimulus.

Summary.

(1) Tetany can occur in "spinal" dogs. It was observed at intervals of from six hours to thirty-six days after mid-dorsal section in five out of six dogs. In a further experiment in which transection was undertaken at the level of the first dorsal segment, tetany occurred in all four limbs.

(2) Tetany in "spinal" dogs occurs in all its three types, tonic, clonic and fibrillary. This is true whether the section be high or low in the dorsal region.

(3) The clonic contractions of tetany tend to be less rapid in the hind-limbs of the "spinal" animal.

(4) In "spinal" dogs the activity of the tetany produced does not appear related to the time of its occurrence after transection of the cord.

(5) The peculiar reflexes of the "spinal" animal were present as early as six hours after transection, when tetany occurred at that time. The activity of the "spinal" reflexes tended to increase with the onset of tetany. "Spontaneous" co-ordinated movements occurred in the hind-limbs. There were distortions of the typical "spinal" reflexes.

(6) The myotatic irritability of tetany is retained in the hind-limbs of the spinal preparation. Myotatic irritability induced by heat was greater in "spinal" than in normally innervated limbs.

PART III.

DE-AFFERENTATION AND TETANY.

The interruption of the afferent nerve supply from one or both hind-limbs was undertaken in four dogs.

The dorsal spinal roots were severed extrathecally, the ventral (motor) roots being left intact. The operation was performed in the lumbar region, on one side in the case of three dogs, and bilaterally in one. In one case decerebration was subsequently performed. Tetany was induced by removal of the thyroid and parathyroid glands, at times

TABLE XI.

Dog	Region de-afferented	Onset of tetany	Condition of affected limb	Control	Condition of control
1.	Left L. 4, 5, 6, 7 and decerebrate	2½ hours	Flaccid. Fibrillary tetany in hamstring	Opposite leg Fore-limbs	Decerebrate rigidity Decerebrate rigidity and clonic tetany
2.	Left L. 4, 5, 6, 7	Some days	No tetany	Opposite leg	Slight clonic tetany
3.	Left L. 4, 5, 6, 7, 8	2½ days	Fibrillary tetany hamstring	Opposite leg	Clonic tetany hamstring
		3 days	Slight clonic ankle and knee. Flaccid	Opposite leg	Active clonic tetany. Clasp-knife rigidity
4.	Left and rt. L. 2, 3, 4, 5, 6, 7, 8 and cut cauda equina	12 hours	Fibrillary left gastroc., left hamstring, right glutei	Fore-limbs and trunk	Fibrillary occasional clonic
		36 hours	Fibrillary, both hind legs	Fore-limbs and trunk	Indifferent fibrillary tetany
		60 hours	Flaccid. Continuous fibrillary	Fore-limbs and trunk	Strong tonic extensor tetany. Continuous, violent clonic and fibrillary tetany

varying from a few hours to three days after the spinal operation. The result of de-afferentation upon tetany is shown in Table XI.

Dog 1.—In this case the left hind-limb was de-afferented by section of the dorsal roots of the 4th, 5th, 6th and 7th lumbar spinal nerves. The animal was in slight tetany at the commencement of and during the operation. Intercollicular decerebration was undertaken immediately after de-afferentation, fibrillary tetany being present in the scalp muscles during its execution. Two and a half hours subsequently, the decerebrate preparation was found to be satisfactory. Decerebrate rigidity was present in the three untouched limbs. Tonic extensor rigidity was very great. No clonic or fibrillary twitches could be seen in these limbs until flexion was undertaken, when both fore-limbs showed clonic jerks. The de-afferented limb was flaccid, but fibrillary tetany was present in the hamstring muscles.

Dog 2.—The area de-afferented corresponded with that in Dog 1. Decerebration was not performed. Subsequently, clonic tetany induced by parathyroidectomy occurred in the fore-limbs and head, and to a less degree in the right (normal) hind-limb. It was entirely absent in the left (de-afferented hind-limb). Tonic and fibrillary tetany did not occur in this dog.

Dog 3.—The dorsal roots of lumbar 4, 5, 6, 7, 8, on the left side were divided. On the third day clonic tetany occurred in the left shoulder region and in the right hind-limb, both in extensor and flexor muscles. One or two twitches were seen in the hamstring muscles of the left hind-limb. In addition, fibrillary tetany was observed in the region of the left ankle. A few hours later very active clonic and fibrillary tetany occurred in both fore-limbs. The dog was placed in a position of dorsal decubitus and the two hind-limbs compared. The right showed very active clonic tetany of the hamstrings, knee extensors and flexors, with short sharp twitches of the flexors and extensors of the pad of the foot; there was also general extensor rigidity. The left (de-afferented) showed slight clonic tetany of the hamstrings, flaccidity of the knee extensors, with occasional added jerks. Very occasional twitches were seen in the ankle extensors and flexors. Contraction of the flexors of the pad of the foot were small (fibrillary) but active. These contractions were of longer duration than those of the right side. The limb as a whole was flaccid.

Dog 4.—The dorsal roots of lumbar 2, 3, 4, 5, 6, 7, 8, were severed on both sides, and the cauda equina cut through below L8. Tetany was precipitated twelve hours after the operation. There were occasional clonic muscular contractions in the fore-limbs, and definite fibrillary tetany, without clonic jerks, in the gastrocnemius muscle of the left hind-limb. Subsequently fibrillary tetany was observed in the muscles of the shoulder and back, in the right gluteal and left hamstring or gastrocnemius muscles. There was occasional clonic jerking in the fore-limb but none in the hind-limb. At thirty-six hours there was definite fine fibrillary tetany in the extensors of the right hip, and in the right and left gastrocnemius. After sixty hours, in head, violent clonic tetany; fore-limbs in continuous tonic extension, very difficult to overcome by passive flexion; continuous additional clonic jerks of violent nature, fibrillary tetany; trunk and shoulders, active clonic fibrillary tetany, remainder, fibrillary tetany only. Hind-limbs completely flaccid throughout; no clonic tetany whatever; continuous fibrillation throughout the musculature of both hind-limbs. The phenomena were observed continuously for fifteen minutes. Later in the third day, clonic tetany occurred in the fore-limbs, but was entirely absent from the hind-limbs.

Analysis of Results.

Of the four dogs, three showed fibrillary tetany in the de-afferented limb. In the one failure tetany was but slight in the opposite control limb. In Dog 1, decerebration did not modify the findings. In Dog 3, on one occasion twitches amounting to clonic tetany were seen in the hamstring muscles of the de-afferented side. With this exception, the tetany observed in de-afferented areas was always fibrillary. In all tetany of this type was observed on five separate occasions, on each of which well-marked tonic or clonic tetany was present in the control limbs. In the case of Dog 4, the contrast between the fore-limbs and the hind-limbs was most strongly marked on all occasions. In this case both hind-limbs had been de-afferented.

Conclusion.

De-afferentation of one or both hind-limbs greatly reduces the activity of tetany. With one temporary exception, in which clonic tetany occurred, the form of tetany in de-afferented muscles has always been fibrillary.

THE WORK AND OPINIONS OF PREVIOUS WRITERS IN RELATION TO THE PRESENT RECORDS.

(1) *Denervation and tetany.* — Paton, Findlay and Watson [1] recorded that peripheral nerve section abolished all "spasms, tremors and jerkings" of tetany. This I found true for fibrillary tetany only if an interval of some twenty-four hours is left for certain unknown peripheral changes to follow upon nerve section.

(2) *Tetany in spinal dogs.*—Carlson and Jacobson [4] found that after high thoracic transection of the cord "extreme parathyroid tetany (epilepsy) does not directly involve the part posterior." In view of this statement, I made a spinal preparation with the transection at the level of the first dorsal segment. Very active tonic, clonic and fibrillary tetany occurred in all four limbs. Luckhardt, Sherman and Serbin [5] mentioned that in chronic spinal preparations, while clonic and fibrillary

tetany are active, tonic tetany is less pronounced below the level of the section, and when present is "in a great measure due to the stimulation of sensory nerves of some part of the animal posterior to the transection." My records show that sometimes the fore-limbs and sometimes the hind-limbs show the more active tonic tetany. The view that the tetany, both tonic and clonic, is contributed to by sensory impulses is supported by its abolition by de-afferentation. Mustard [2] also states that the epileptic (*sic*) spasms of parathyroid tetany do not develop posterior to a spinal transection, and regards this as evidence of a dependence of tetany upon certain higher centres. I was unable to find a constant difference between the manifestations of tetany above and below the level of spinal sections.

(3) *Spinal reflexes and tetany.*—Luckhardt, Sherman and Serbin [5] recorded the great increase in reflex irritability of spinal dogs in tetany. They also noted the reduction in the period of spinal shock. Further, they noted the appearance of new and unusual reflexes. They state that animals in tetany were hypersensitive to strychnine. Carlson and Jacobson [4] mention reflex hyperexcitability as a feature of tetany. These observations were confirmed, with the exception of the strychnine effect, which was not examined.

(4) *Tetany and de-afferentation.*—Mustard [2] records de-afferentation of one hind-leg as leaving "slight twitchings" when tetany supervenes. This coincides with my observations.

(5) *Hyperexcitability of peripheral nerve trunks.*—Falta [11] quotes von Frankl-Hochwart to the effect that Trousseau's phenomenon depends upon the excitability of the nerve trunks themselves, and that tetany can result bilaterally from pressure on one brachial plexus. He further quotes Schlesinger as saying that only "mixed nerves" containing sensory fibres can excite tetany. These observations are of interest in association with my finding of contractions of the opposite leg on mechanically stimulating the exposed sciatic nerve in a spinal preparation. I cannot offer an explanation of this phenomenon.

SUMMARY.

(1) The lowest reflex spinal arc is requisite to the full muscular manifestations of canine parathyroid tetany. If this arc be interrupted on its afferent side by dorsal root section the grouping and synchronization of the contractions are minimal, and *fibrillary* tetany results. But if the arc remain intact, the contractions of the fibres are either synchronized into violent clonic muscular jerks (*clonic* tetany) or show

maintained contraction (*tonic* tetany). Both types of contraction may occur contemporaneously in the same limbs, and clonic jerks may be present in a muscle which exhibits tonic tetany (Parts I and III).

(2) All the elements of tetany are retained in the hind-limbs when the spinal cord has been transected in the cervical or dorsal region. It is not found that impulses from higher centres add anything to the pattern of canine tetany. Tetany shortens the period of "spinal shock" and increases the activity of "spinal" reflexes. The myotatic irritability of the transverse spinal preparation is also increased by tetany (Part II).

(3) Fibrillary tetany is tetany in its simplest form. While an intact spinal-cord reflex arc is essential to the development of the clonic and tonic forms of tetany, fibrillary tetany persists if the motor connections between the spinal cord and the muscle remain intact. Muscles which have been completely denervated for a few days do not develop fibrillary tetany (Part I).

(4) Fibrillary tetany is not abolished by denervation until about twenty-four hours after section of the nerve of supply; thenceforward it is entirely absent. This implies that fibrillary tetany depends upon a circulatory factor acting upon an intact peripheral mechanism, the function of which is critically altered, not at the time of nerve section, but some twenty-four hours subsequently (Part I).

(5) The electrical hyperexcitability which characterizes muscles in tetany is exaggerated in the early stages (first few hours) after section of the nerve of supply. On about the fifth day after section an independent electrical irritability characteristic of denervation sets in. At this stage tetany does not lower the electrical threshold, but rather tends to raise it (Part I).

CONCLUSIONS.

The essential feature of tetany appears to be the action of a circulatory factor peripherally upon some site in the muscle, to cause repeated contractions of individual muscle fibres and electrical hyperexcitability. Both this fibrillary tetany and the electrical hyperexcitability are influenced by the nerve supply from the central nervous system. Given the integrity of the spinal reflex arc, the muscular contractions are synthesized into the characteristic forms of "tonic" and "clonic" tetany. In the presence of only the motor supply from the spinal cord the contractions remain fibrillary in type, but electrical hyperexcitability persists. Complete denervation leads to the following sequence of events: At first there is continuation of fibrillary tetany and increased electrical excitability with the onset of tetany. This probably corresponds to a phase of early degeneration at some point of action within the muscle which maintains its irritability to the circulatory factor of tetany, and increases the normal effect of the latter on direct electrical excitability. Subsequent degenerative changes lead successively to the loss of the fibrillary response to the circulatory factor and the institution of a peculiar electrical excitability of degeneration which is independent of tetany.

If this interpretation is correct, parathyroid tetany arises essentially from the action of a changed circulation upon muscles. The point of action depends upon an intact motor nerve supply for its function, and undergoes successive changes of threshold on denervation. An intact spinal reflex is required to convert essential or fibrillary tetany into its elaborate clonic and tonic forms. Impulses from nervous centres higher than the spinal cord are not requisite to these forms of canine tetany.

Neither the effects of tetany on conduction through the central nervous system itself, nor the nature of the circulatory changes acting peripherally, have been studied.

The "final common point" in muscle excitation.—If the foregoing interpretation of the neuromuscular mechanism of tetany be accepted, this disease draws attention to an interplay of nervous and circulatory factors to produce effects at what might be called a "final common point" of synthesis of influences affecting muscular contraction. Other examples of the twin importance of circulatory and nervous factors in affecting this final point of stimulation of muscle are the actions of circulating drugs in enhancing, depressing or modifying the effects of nervous stimulation (e.g. the selective peripheral actions of curare [12] and physostigmine [13]) on the one hand, and, on the other, the effect of denervation on the response of muscle to drugs (e.g. acetyl choline [14]).

Diseases other than tetany, in which altered circulatory states might diminish or increase the effect of nervous stimulation of muscles, are not discussed in this paper.

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LOCALIZATION OF THE SLEEP MECHANISM[1].

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INTRODUCTION.

THE value of hypersomnolence as a localizing symptom is still somewhat uncertain. The determination of this point, as well as the understanding of the mechanism of pathological and normal sleep, may obviously be greatly furthered by the investigation of cases of brain tumour associated with disturbances of the sleep rhythm. For these reasons the present clinico-pathological study of three cases of diencephalic tumour has been undertaken. In two of these hypersomnolence was a prominent clinical feature, while the third, in which there was no sleep disturbance, is included for purposes of control and comparison.

To provide a basis for the evaluation and discussion of the cases a brief review of some of the concepts of normal and pathological sleep and of the evidence upon which these concepts are based seems advisable.

NORMAL SLEEP.

Normal sleep, Kleitman [1] believes, is characterized by three criteria: (1) a loss of critical reactivity to events in the environment, (2) an increased threshold of general sensibility and reflex irritability, and (3) an ability of being aroused or brought back to wakefulness. Trömner [2] defines sleep as a primitive, periodic, instinctive life process which can be aroused by many different means, and which serves to rest the cerebrum while permitting bodily regeneration and growth. Pette [3, 4] regards the sleep-wake rhythm as an elementary vegetative process necessary to life and similar to temperature regulation or water metabolism. All writers agree that the exact nature of the sleep process is still unknown, but certain characteristics of normal sleep

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have been observed and form in part the basis for such definitions as are given above. It has been pointed out (Trömner [2]) that the phenomena occurring during sleep may be grouped as follows: (1) autonomic effects, such as a slight rise of temperature, lowering of blood-pressure, sweating, slowing of the pulse, lowering of the metabolic rate: (2) "active" or stimulatory effects, including myosis, changes in the position of the eyes, yawning; (3) inhibitory effects, particularly mental and emotional inhibition, and the slowing of some of the secretory activities; and (4) dissociation effects, such as dreams, and the changes associated with partial awakening. It is well established that sleep is influenced by a great variety of factors, including afferent exogenous stimuli, cortical processes, endocrine changes and activity of the autonomic system. On the basis of such knowledge it has seemed probable to many writers that a central control for the sleep-wake rhythm exists, and from the apparent similarity of the process to known vegetative functions which are closely related to the interbrain it has seemed reasonable to many to postulate a sleep centre in the diencephalon.

Finally, experimental and clinical experiences have done much to confirm this conclusion reached on theoretical grounds. It has been shown by Karplus [5] that in decerebrate animals the normal sleep rhythm is preserved. Lesions of various types located in the diencephalon or mesencephalon has been found associated with hypersomnolence. Experimental damage and experimental stimulation of portions of the interbrain have produced abnormal sleep states in animals. The rather localized effect of certain soporific drugs upon the interbrain has been demonstrated. These data, even though dealing with excessive sleep for the most part, have resulted in the obvious inference that any area controlling pathological somnolence must also play an important role in the normal sleep rhythm, and they consequently form an important part of our knowledge concerning sleep.

REVIEW OF THE LITERATURE.

A survey of the previous reports related to sleep disturbances associated with cerebral lesions tends to be somewhat confusing, due largely to the rather wide disagreement as to the exact localization of the central sleep-controlling mechanism. It seems probable that some of the divergence of opinion may be the result of difficulties in the selection of clinical cases of hypersomnolence. A truly hypersomnolent individual not only sleeps a greater portion of the twenty-four hours than the average but falls asleep in the presence of stimuli, such as conversation, reading and even eating, which ordinarily maintain a waking state. Furthermore, the sleep is always characterized by its reversibility, i.e. the ability to be aroused to a state of essentially normal mental and physical capacity by stronger stimuli, such as calling by name, shaking, or questions. As a further explanation of the differing opinions of various workers there are certain additional factors inherent in the different approaches to the problem. Following a survey of the evidence relating to hypersomnolence these may be considered in presenting a brief summary of the previous work on the subject.

It is convenient to consider the work of other writers in three groups, based upon the type of pathology involved: (1) inflammatory, (2) neoplastic, and (3) experimental lesions. It is true that traumatic, degenerative and vascular changes associated with hypersomnolence have been reported (Stertz [6]), but since none of this group of cases has been of importance in the closer localization of the sleep mechanism, they will not be considered here.

(1) *Inflammatory lesions of the brain associated with hypersomnolence.*—Mauthner [7] (1890) was among the first to suggest that the diencephalon exerted a control over sleep, this conclusion being based upon his observation that the majority of the pathological changes in the brain of an encephalitic patient who had shown hypersomnolence lay in the interbrain. Similar studies on many more cases, seen in the early years of this century and subsequent to the influenza epidemics of 1918 and 1920, led Economo [8] to essentially the same conclusion. He went further however and postulated a central sleep mechanism occupying the gray matter about the caudal portion of the third ventricle and the rostral end of the aqueduct, lying close to the nucleus for the third nerve ; he emphasized the frequency with which sleep disturbances and abnormalities of the oculomotor nerve form the principal symptoms of epidemic encephalitis.

In addition to these studies of encephalitis a number of reports of purulent collections and of meningitis have appeared. Luksch [9] (1924) tended to confirm the opinions of Economo, in reporting a case of subacute bacterial endocarditis with hypersomnolence, in which autopsy revealed a suppurative lesion involving the posterior portion of the third ventricle and its walls, and the structures about the upper end of the aqueduct. In the same year Adler [10] found multiple abscesses in the hypothalamus and the periventricular gray matter around the third ventricle in a very similar case. Other areas of the interbrain were implicated, however, by Hirsch [11, 12] (1924, 1928), who found, in studying four cases with sleep disturbances, lesions between the anterior and posterior commissures in one, in the pulvinar near the posterior commissure in two, and in the dorsal gray matter of the rostral portion of the aqueduct in a fourth. Still another region of the interbrain apparently related to hypersomnolence was described by Marinesco and his associates [13] (1928), who reported upon two patients suffering with tuberculous meningitis who showed excessive sleep. Subsequent pathological observations showed the tubo-infundibular region to be badly damaged—in part as the result of interference with its blood supply.

(2). *Cerebral tumours associated with hypersomnolence.*—Since Sinkler [14], in 1893, described a case of brain tumour involving the diencephalon in which hypersomnolence was a prominent symptom many similar reports (references [15] to [29] inclusive) have appeared in the literature. The early papers, based usually upon cases in which rather large tumours were found, are marred by the absence of careful description of the exact location of the lesions. Soca [15], in 1900, noted hypersomnolence in a case with a tumour in the infundibular region. On the other hand, Salmon [16] (1906) believed that the destruction of the hypophysis, or of the infundibular stalk or its connexions, was responsible for the appearance of pathological sleep in cases he observed. Other evidence seemed to point not to a single diencephalic area, but to the entire interbrain. François and Vernier [17] (1919) for example, observed a woman of 38 who suffered with marked somnolence for four months prior to her death. Autopsy revealed a large tumour, apparently originating from the base of the brain between the chiasm and the cerebral peduncles and growing upward to the corpus callosum, and lateralward to include the entire diencephalon and reach the lateral ventricles. Weisenberg [18] (1911), in reviewing all the reported cases of tumour arising within the third ventricle, noted four in which somnolence was a prominent symptom.

Fulton and Bailey [19] (1929) reported an unusual and important case. A woman of 28, who had had attacks of drowsiness for four or five years, was found at necropsy to have a small tumour (2 by 1·5 cm.) in the floor of the third ventricle involving the infundibulum at its dorsal end, almost the entire tuber cinereum and the mammillary bodies, but not encroaching upon the ventricular system sufficiently to cause intracranial hypertension. In three additional cases with hypersomnolence they found in one a small gelatinous cyst (17 mm. in diameter) attached to the roof of the third ventricle and lying within it; in another a solid tumour filling the ventricle, and in the third a very widespread pinealoma involving practically the entire diencephalon. In view of the varied nature of their cases as well as those in the literature these authors did not feel that it was possible to speak of a sharply localized sleep centre in the diencephalon, in spite of the clear-cut clinical picture and the sharply localized infundibular, tuber and mammillary lesion in their first case.

Additional evidence concerning the importance of various hypothalamic areas was furnished by the work of Marinesco and his associates [13, 20]. In 1929 these workers reported a comparative study of two cases with marked internal hydrocephalus, dilatation of the third ventricle and consequent lesions in the floor of the ventricle. In one of these the changes occurred in the right retro-thalamic region, beneath the corpus callosum and limbic convolution above, the cerebral peduncles in front, and extended into the cephalic portion of the mesencephalon where the gray matter surrounding the aqueduct was involved and the iter completely occluded. This patient showed marked hypersomnolence. The control case showed at autopsy a large tumour of the left cerebellar hemisphere and the vermis, with occlusion of the fourth ventricle, hydrocephalus with damage to the infundibular area, but no changes around the aqueduct. As a result of the study of these cases, and those of meningitis described above, this group of workers concluded that the sleep mechanism consists of a series of connected centres beginning in the infundibular region and extending caudally into the upper portion of the mesencephalon. They suggested also that damage to a portion of this series might be compensated for by the remainder of it.

Hechst [21] (1929) was to a considerable extent in agreement with this opinion, and concluded, after a careful clinico-pathological study of four cases of diencephalic tumour associated with hypersomnolence, that the medial portion of the thalamus and the gray matter around the caudal part of the third ventricle and the rostral end of the aqueduct play about equal roles in the sleep mechanism. Since the tumour in one of his cases occupied only the left thalamus, Hechst believed that hypersomnolence can result from unilateral lesions.

In his two reports of seven cases with interbrain tumour Weisz [22, 23] made one of the most important recent contributions to the study of sleep. Like Hechst and Marinesco his conclusions as to the exact location of a central sleep mechanism were guarded. From the clinical standpoint he felt that no syndrome of the third ventricle region could be drawn up, but he was impressed by the hypersomnolence present in all of his cases. On the basis of the study of serial sections of the diencephalon in six instances, he stated that no closely localized centre for sleep can yet be postulated, although his evidence suggested that lesions in the rostral portion of the hypothalamus near the tuber cinereum were most important in the production of sleep disturbances. This author also pointed out that vascular disturbances beyond the limits of the tumour proper may be responsible for the hypersomnolence.

(3) *Experimental studies.*—The experimental production of sleep has been carried out both by stimulation and destruction of diencephalic tissue. Hess [30, 31], in 1927, using a very light electrical stimulus, was able to produce sleep in animals when he stimulated the periventricular gray matter near the massa intermedia and near the cephalic portion of the aqueduct, and the head of the caudate nucleus. He noted that the stimulation of the more ventral portion of the periventricular gray matter resulted in deeper sleep, and that the more lateral irritation resulted in sleep coming on some moments after the cessation of the stimulus.

Spiegel and Inaba [32, 33] on the other hand obtained similar results by introducing needles into the thalamus bilaterally. Puncture of the periventricular gray matter did not produce sleep in their animals.

A third method of approach to the question was used by Beattie, Brow, and Long [34]. In studying the cerebral autonomic connections these workers were able to produce sleep in cats by making a cut (1 by 4 cm.) from the anterior edge of the colliculi to the posterior edge of the pituitary fossa. These animals showed hypersomnolence after operation, as well as hypopyrexia, glycosuria, polyuria, albuminuria and contracted pupils.

In 1927 a new line of experimental attack on the problem was described by Demole [35]. He found that the injection of certain solutions, particularly calcium chloride, into the infundibular region in cats produced a characteristic sleeping state for varying periods of time. Potassium chloride had an opposite exciting effect, which could be to some degree inhibited by the later injection of the calcium salt. Similar changes, although more slowly produced, followed the intraventricular or intracisternal injections of these solutions. A number of later workers, including Cloetta and Fischer [36], LaFora [37], and Marinesco [38, 39], have confirmed the results obtained by Demole from intracerebral injections. Marinesco and his group of workers summarized the results of their very extensive experimental studies as follows: (1) Puncture of the wall of the third ventricle of the cat produces a true sleep which is reversible. (2) The intracerebral injection of calcium chloride into the diencephalon favours sleep; potassium chloride injection inhibits sleep. (3) Polarization of the infundibular region, using the cathode polarization, inhibits sleep. (4) The intraventricular injection of calcium chloride results in sleep. (5) Intracerebral injection of choline, and sometimes potassium chloride, produce sleep which is preceded by agitation and muscular hyperactivity. (6) In all cases of experimental sleep in animals lesions were constantly found in the lateral walls of the third ventricle.

Keeser and Keeser [40, 41] were able to confirm in a slightly different way the theory of the importance of the action of certain chemicals upon the diencephalon in producing sleep. They succeeded in combining barbituric acid derivatives and ferric chloride and administering them to animals in large doses. The animals exhibited the usual soporific effects of the barbiturates and were then killed. Upon staining sections of the hardened brains with potassium-ferrocyanide the presence of the greater portion of the barbituric acid derivatives in the interbrain was clearly demonstrated, and suggested strongly that this was the site of action of the drug in producing sleep.

A final piece of evidence favouring a chemical or hormonal change in the sleep state was furnished by Kroll [42]. He found that acetone extracts of brains of sleeping animals produced characteristic sleep states when injected intracisternally or intravenously in cats. Whether the original sleep was produced artificially by any of the known methods or resulted sponanteously or from hibernation made no difference in the results.

To condense and clarify the data presented in this survey of the evidence related to a central sleep mechanism a brief summary is helpful. At the same time some of the difficulties involved in each method of attack on the problem may be mentioned.

(1) *Studies based on inflammatory lesions.*—Based chiefly upon cases of encephalitis, but also upon instances of embolic abscesses and meningitis, it has been suggested that the sleep mechanism is to be found: (1) in the periventricular gray matter of the third ventricle, (2) in the caudal portion of the hypothalamus and the cephalic end of the mesencephalon, (3) in the dorsal gray matter over the cephalic end of the aqueduct, (4) in the thalamus, and (5) in the region of the

infundibulum and tuber cinereum. These data are open to several comments. The lesions are in all cases widespread, and the assumption that one involved area rather than any other is responsible for the production of sleep disturbances is dangerous. The psychic changes and the general toxic effects which are present in some instances (as in cases of subacute bacterial endocarditis, or in meningitis) may considerably confuse the clinical picture. It should be noted also that in epidemic encephalitis not only does hypersomnolence occur, but inversion of the sleep rhythm, insomnia and dissociation of mental and bodily sleep (Economo). The absence of these symptoms in cases in which other lesions involve the same areas suggests that these particular sleep disturbances may be related to the character of the lesion as well as its location.

(2) *Studies based upon brain tumours.*—The many reports of brain tumour cases indicate that the sleep mechanism may be localized variously in: (1) the thalamus; (2) the hypophysis; (3) the infundibular region; (4) the caudal portion of the hypothalamus; (5) the cephalic end of the mesencephalon; (6) a chain of centres extending from the infundibular region caudally through the hypothalamus to the aqueduct. The most important failing of this body of evidence is the paucity of presentations including careful localization of the lesion. On several of the more complete reports certain other comments may be made. In considering the work of Weisz, for example, one is impressed by the large size of the lesions found. In three instances the tumour occupied the greater part of one hemisphere, and in three cases there was extensive hæmorrhage in and about the tumour. In the presence of such widespread disease one may question again the propriety of the study of only the hypothalamus on the assumption that the damage to this area is responsible for the sleep disturbances noted. In many reports the possible effects of increased intracranial pressure or very marked hydrocephalus may impair the validity of the conclusions. A striking exception is the case of Fulton and Bailey, where the clinical picture was very definite, the pathological study was complete, and the lesion was small and did not obstruct the ventricular system. This tumour occupied the infundibular region and the tuber cinereum, and encroached on the mammillary bodies.

(3) *Experimental studies.*—Curiously enough, experimental studies have led to more confusing results than the clinical reports. The evidence at hand suggests localization of a sleep-controlling area in: (1) The infundibular region; (2) the periventricular gray matter of the

third ventricle; (3) the thalamus; (4) the cephalic portion of the mesencephalon; and (5) the head of the caudate nucleus. The inconclusive nature of this work may be due in part to the difficulty of interpreting the clinical picture in animals. It is interesting to note, for example, that an attack of sleep is produced in experimental animals by a lesion or stimulus—a state of recurring hypersomnolence such as is found in humans not having been reported. It is evident, too, that to produce a lesion in any subcortical area the brain tissue intervening between this area and the surface must be to some extent injured. Marinesco has suggested that the production of large experimental lesions may cause sufficient stupor from operative shock as to obscure a brief period of somnolence.

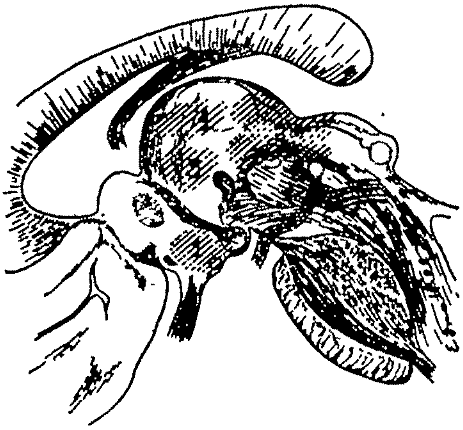

FIG. 1.—Diagrammatic representation of the areas which are closely related to sleep disturbances, as evidenced by the studies in the literature. 1, The infundibular and tuber region; 2, the gray matter around the rostral end of the aqueduct; 3, the periventricular gray matter of the third ventricle; 4, the thalami.

Considering, then, the previously reported work relating to the localization of the sleep mechanism in the light of certain difficulties and possible sources of error, one may say that there is considerable reliable evidence favouring four areas in the diencephalon as being important in the production of hypersomnolence (fig. 1): (1) the infundibular and tuber region (supported by the cases of Fulton and Bailey, and Weisz); (2) the periventricular gray matter (supported by the experimental work of Hess and Marinesco chiefly); (3) the gray matter surrounding the cephalic portion of the aqueduct (supported by Economo's studies); and (4) the medial portion of both thalami (supported by the experiments of Spiegal and Inaba).

MATERIALS AND METHODS.

The pathological studies in the three cases reported here were carried out in the following manner. Fixation was in formalin. Blocks of the tissue were cut to include the tumour and surrounding structures; these were imbedded in celloidin and cut in serial sections. Alternate fifth sections were stained by means of Weil and by hematoxylin eosin.

In any discussion of the diencephalon the variations in anatomical nomenclature tend to cause confusion. In the present report the simpler classifications of thalamic and hypothalamic structures have been given preference, in part because of the difficulty in recognizing the smaller nuclear groups without special stains, and in part because of the lack of evidence that the many minute morphological nuclei which have been described by some authors have any functional or physiological identity as units. Accordingly the terminology of LeGros Clark [43] has been used in describing the thalamic lesions and the descriptions of Malone [44, 45] are followed in referring to the hypothalamic nuclei. For reference purposes several anatomical studies of other authors (references [46 to 52] inclusive) have been included in the bibliography.

CASE REPORTS.

Case 1 (*file number* 24813). *History.*—E. G., a 47-year-old miner, had been entirely symptom free until sixteen days before his admission. Two days previous to the onset he was struck on the head by a falling piece of coal, but noted no immediate ill effects. His first symptoms—severe headaches, blurred vision and dizziness—all coming on in attacks of several hours' duration two or three times daily, were sufficiently marked to necessitate stopping work.

Eight days prior to admission an attack of generalized tremor occurred, and on the same day mild mental changes, such as disorientation, impairment of memory and possibly visual hallucinations developed. The past history and family history revealed nothing significant..

Examination.—It was apparent that the patient was disoriented and could remember little of recent events. A generalized motor weakness and moderate ataxia of both upper and lower extremities were present. Examination of the cranial nerves showed a left external rectus palsy, bilateral choked discs and a diminution of hearing on the left. A left-sided Babinski reflex was noted.

Sleep disturbance.—On examination the patient's hypersomnolence was striking. He could be aroused by calling his name, by repeated commands, or by painful stimuli, but in the course of a few minutes would fall asleep again.

Course.—Because of the clear-cut history of antecedent trauma a chronic subdural hematoma was suspected, but when bilateral trephine openings failed to disclose this a right temporo-parietal bone flap was reflected. No tumour was seen in this area, and the discovery that the right ventricle was very large led to the suspicion of a deep-seated, midline lesion, and the wound was closed. The patient seemed profoundly shocked, even though loss of blood had been slight and all intracranial hypertension had been relieved. He died four hours after operation.

Gross pathology.—The external appearance of the brain was normal. On sectioning the specimen, however, a moderate degree of internal hydrocephalus involving both lateral and the third ventricles was apparent. In the pineal recess lay a tumour mass measuring 2·5 by 1 cm., which extended anteriorly into the third ventricle, laterally into the thalami, and caudally to about the middle of the superior colliculi. Ventral to the lesion the roof structures of the anterior end of the aqueduct were compressed and invaded. The tumour appeared to be infiltrative, showed a granular cut surface, and was somewhat softer than the surrounding brain.

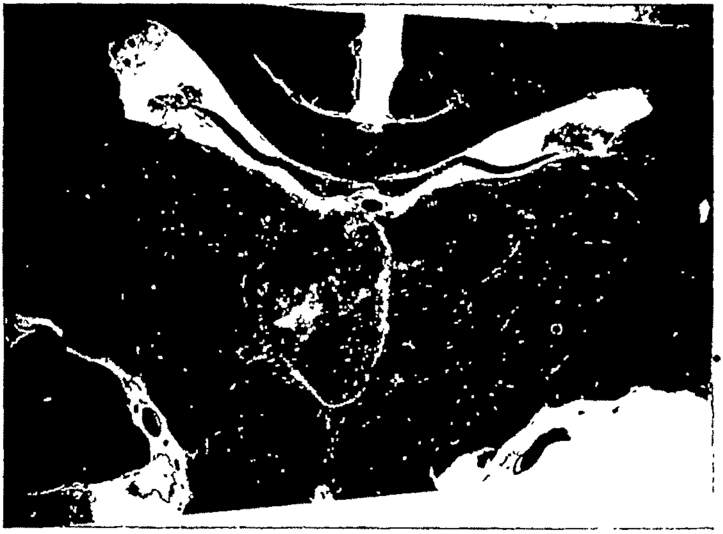

FIG. 2.—*Case* 1. The tumour is seen occupying the third ventricle, periventricular gray matter and the medial nuclei of both thalami, at the level of the caudal portion of the diencephalon. The centre-median nucleus and the external geniculate body are prominent on the right.

Microscopic pathology.—At the level of the oral end of the red nucleus the tumour could be seen projecting into the third ventricle, but not yet invading its walls. This invasion began in the immediately succeeding sections in the periventricular gray matter, the "centre median" and ventral thalamic nuclei, and the thalamic fasciculus on the right. More caudally, in sections containing the oral end of the lateral geniculate body, the lesion enlarged to occupy a portion of the right dorsomedial, "centre median," and ventral nuclei, and a thin strip of periventricular gray and "centre median" nucleus on the left. At the level of the corpus Luysi the tumour appeared considerably larger and occupied a greater portion of the same thalamic nuclei as before. Ventrally, however, it did not invade the red nucleus or the arcuate nucleus, extending only into the most dorsomedial of the fibres surrounding the red muscles. Caudal to the corpus Luysi the tumour was almost symmetrical; it obliterated the third

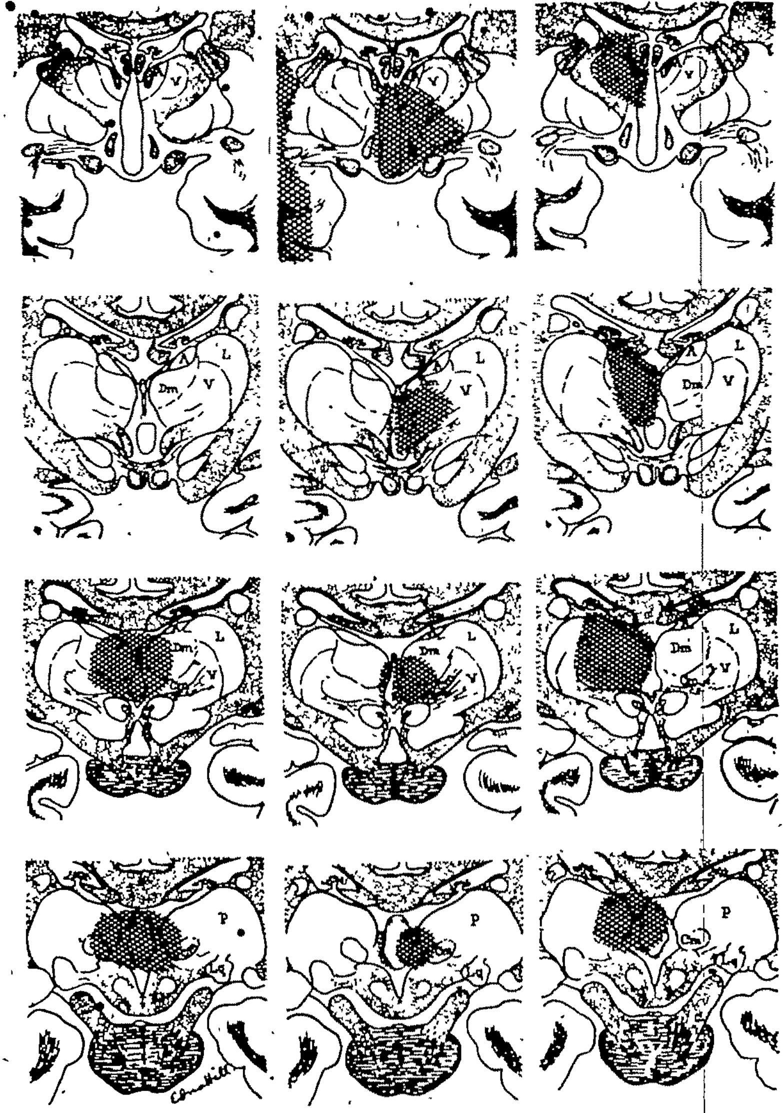

FIG. 8.—Diagrams illustrating the positions of the lesions at four levels of the diencephalon in each of the three cases. A, Anterior thalamic nucleus. V, Ventral thalamic nucleus. L, Lateral thalamic nucleus. Dm, Dorso-medial nucleus. Cm, Centre median nucleus. P, Pulvinar. Lg, Lateral geniculate body.

ventricle, spread out to occupy most of the "centre median," three-fourths of the dorsomedial, and the medial extremity of the ventral nucleus on both sides. Again the lesion remained dorsal to the red nucleus and its surrounding fibres. The fasciculus retroflexus was destroyed bilaterally at this level. In the sections caudal to this point the ventral portion of the habenula was involved on both sides as well as the medial aspect of the putamen, but otherwise there was little change in the lesion. As the tumour decreased in size it became more dorsal and disappeared soon after its invasion of the posterior commissure.

Summary of pathology.—Microscopic study showed the tumour to be a glioblastoma multiforme, filling the caudal one-third of the third ventricle and the pineal recess. The lesion began at the level of the rostral end of the red nucleus, and extended beyond the posterior commissure to invade the rostral tip of the mesencephalon. Laterally the periventricular gray matter and the thalami were infiltrated bilaterally, the dorsomedial nucleus being principally involved, with less invasion of the "centre median" and the ventral nuclei. Farther caudally the pulvinar and habenula was infiltrated and compressed on both sides. Ventrally the lesion penetrated the periventricular gray matter and reached the medial lemniscus bilaterally. The posterior commissure was infiltrated.

Case 2. *History.*—J. C., aged 50, gave a history of having been troubled first with persistent hiccoughs for one week in 1928, again for one week in October, 1931, and finally almost constantly during the three weeks preceding his admission on December 18, 1931. During the months of November and December marked mental deterioration had occurred, the patient becoming confused, apathetic and unable to remember such simple facts as his age or the names of his friends and visitors. The past history and family history revealed nothing unusual, although an attack of influenza in 1926 was noted.

Examination.—The mental failure was marked. The patient was disoriented for time, depressed, apathetic and unable to perform even the simplest arithmetic. He could not remember the name of the President or the discoverer of America. He had forgotten his age, and could not recall what he had done a few minutes before. Neurological examinations were entirely negative at first, though later a slight exaggeration of the right tendon reflexes and some ataxia of the left arm were noted. Lumbar puncture showed normal pressure and normal cerebrospinal fluid.

Sleep disturbances.—Hiccoughs and hypersomnolence were the two most striking symptoms of this patient. He slept frequently during the day even at the time of admission, and these periods of sleep became more frequent during his stay. He could be aroused readily by questions, noises or painful stimuli.

Course.—The patient was thought to be suffering with epidemic encephalitis. In spite of a variety of therapeutic measures his hiccoughs continued, his mental state and hypersomnolence grew worse, and about one month after admission he grew stuporous and died from a terminal bronchopneumonia.

Gross pathology.—In the left frontal lobe beginning at the genu of the corpus callosum was found a tumour mass about 3 cm. in diameter, occupying chiefly the third frontal convolution, but spreading into the second frontal gyrus and the operculum. In the right side another tumour occupied the head of the caudute nucleus, causing a marked enlargement of this structure which spread out into the ventricular cavity (right lateral ventricle). It extended backward, occupying pallidum, putamen and the entire right thalamus, and infiltrating all of the internal capsule except a small portion of the genu. Laterally it spread out to involve the claustrum and compress the external capsule, insula and temporal lobe, particularly the region of the hippocampus. Medially at the level of the beginning of the iter the lesion crossed to the left side and invaded the left thalamus and gray matter around the upper end of the aqueduct. Ventrally the right corpus subthalamicum was infiltrated and the right corpus mammillare was slightly enlarged. The red nucleus and substantia nigra were not invaded. The third ventricle was compressed and apparently entirely obliterated posteriorly by the tumour, and the right anterior horn was encroached upon. Both posterior horns of the lateral ventricles were distended. The corpus callosum was slightly thinner than normal.

Microscopic pathology.—In the serial sections it was apparent that the two tumours described were connected and formed parts of one bilateral, very irregular and highly infiltrating tumour, which proved to be a glioblastoma multiforme. However, since the tumour mass on the left lay for the most part outside tho diencephalon, and was to a large extent a separate lesion, the description may be justifiably simplified by describing it briefly as a distinct neoplasm.

The left-sided tumour appeared in the serial sections, which began at the level of the anterior commissure, in the cortex and subcortical tissue of the frontal lobe and insula, and spread mesially to involve claustrum, external capsule, and the lateral border of internal capsule and putamen. Ventrally it extended through the putamen to join the tumour tissue from the opposite hemisphere. In the succeeding sections this lesion grew smaller gradually and extended farther ventally to involve a portion of the temporal lobe. Caudal to the insula the tumour was considerably diminished in size and formed a narrow subcortical strip from the internal capsule above to the temporal cortex below. Slightly caudal to the mammillary bodies the extension of the neoplasm, now a separate mass, could be seen in the globus pallidus, disappearing at the level of the red nucleus.

The diencephalic tumour mass lay principally on the right, but throughout the sections was to some extent bilateral. At the level of the anterior commissure it occupied the medial one-third of internal capsule, the entire pallidum and the ventral portion of putamen on the right. On the left the invasion was less extensive but included periventricular gray matter, globus pallidus, anterior commissure and to a slight extent the internal capsule. At a level just rostral to the chiasma the medial portion of the anterior and ventral thalamic nuclei, the ventromedial one-third of internal capsule, almost the entire globus pallidus, and the medial border of the putamen were occupied by tumour on the right. The sublenticular area was infiltrated. Medially the tumour spread through the third ventricle (and its periventricular gray matter on both sides) to involve the medial border of the thalamus, the internal capsule, and a considerable portion of the globus pallidus on the left. Between the tuber cinereum and the mammillary bodies the right thalamus and hypothalamus were extensively damaged. The dorsomedial and anterior nuclei were slightly infiltrated, the ventromedian half of ventral and a small portion of lateral nuclei, the internal capsule, all of the hypothalamus (including n. paraventricularis, n. supraopticus, and n. tuberis lateralis), and the dorsal portion of temporal lobe were occupied by tumour on the right side at this level. The periventricular gray and most of the third ventricle were obliterated and the left dorsomedial and ventral nuclei, the medial extremity of internal capsule and the medial half of pallidum were involved. N. paraventricularis and n. supraopticus were invaded slightly but not destroyed on the left. In the sections through the mammillary bodies the tumour was somewhat smaller. The medial one-third of the right thalamus, including about this proportion of dorsomedial and ventral nuclei, was obliterated. More ventrally the periventricular gray matter, n. paraventricularis, field of Forel, zona incerta and the mammillo-thalamic tract were infiltrated. The dorsal portion of the mammillary nuclei and the n. tubero-mammillaris were invaded, but preserved relatively normal architecture. Spreading across the third ventricle the tumour involved a crescentic area about 1 to 5 mm. in width in the left ventricular wall, including the medial portion of dorsomedial and ventral nuclei, the dorso-

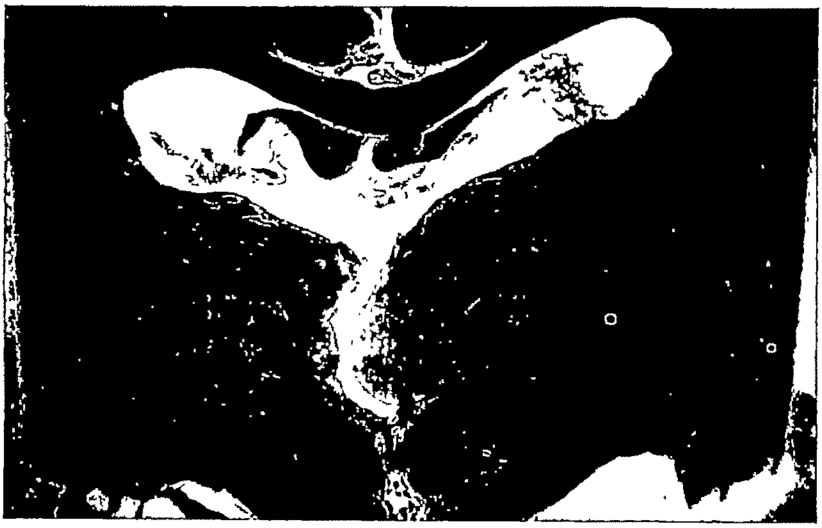

FIG. 4.—*Case 2.*—Section through the oral tip of the left red nucleus showing the tumour growing from the medial portion of the right thalamus, and involving the periventricular gray matter and the medial thalamic nuclei on the left.

medial border of mammillo-thalamic tract, the periventricular gray matter, and n. paraventricularis. In sections through the rostral portion of the red nucleus the tumour was still smaller; it occupied a small portion of dorsomedial nucleus, all of "centre median" nucleus and the medial third of ventral nucleus on the right. Ventrally it invaded the field of Forel, zona incerta and the dorsal border of body of Luys, but did not involve the red nucleus. The extension across the midline lay in the periventricular gray matter, most of the "centre median" nucleus, the medial portion of dorsomedial and ventral nuclei. The tumour here lay entirely dorsal to the field of Forel. Caudal to this level the neoplasm diminished rapidly in size, lying in the dorsomedial (right) and "centre median" nuclei (bilateral), until its disappearance at the level of the external geniculate body.

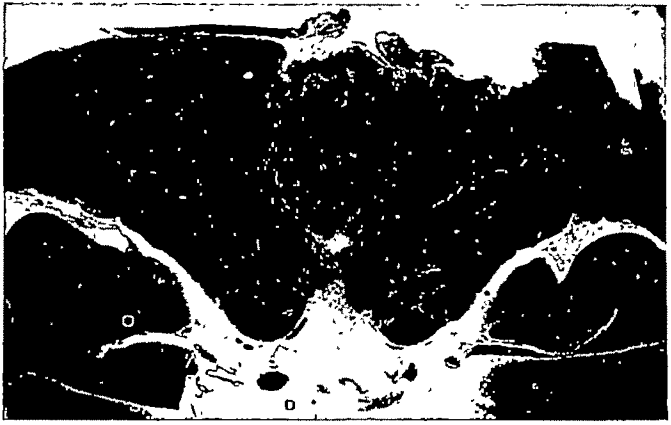

FIG. 5.—*Case* 3.—Section at the level of the oral end of the red nuclei, the tumour being seen in the medial half of the left thalamus (the section is viewed from the front so that the left thalamus is seen on the right) and filling the third ventricle almost completely. There is some compression but only very slight infiltration of the right thalamus.

Summary of pathology.—The irregularly shaped, highly infiltrating glioblastoma multiforme seen in the sections of this case consisted of two connected, roughly spindle-shaped masses of tumour. One lay superficially in the left hemisphere, extending from the second frontal convolution at the level of the genu of the corpus callosum through the insula (where it formed a band of tumour bordered dorsally by the internal capsule and ventrally by the temporal cortex) and globus pallidus, to end at the level of the red nucleus. The other, beginning chiefly in the head of the right caudate nucleus, but lying so near the midline as so involve the medial portion of both hemispheres throughout its length, extended through the medial portion of right pallidum, internal capsule, thalamus and hypothalamus to end at the level of the red nucleus and the external geniculate body. The third ventricle and medial portion of the left thalamus were involved between the same levels (figs. 2 and 4).

Case 3 (*file number* 27875).—This case is included for the purpose of control and comparison, disturbances of sleep being entirely absent despite the presence of a diencephalic tumour. Accordingly the clinical history and details of the lesion will be omitted.

Summary of pathology.—Study of the brain in this case showed a spindle-shaped astrocytoma occupying the left diencephalon, extending from the level of the anterior columns of the fornix to the rostral portion of mesencephalon. Beginning in the wall of the left lateral ventricle the tumour lay chiefly in the third ventricle and dorsomedial part of the left thalamus, including anterior, ventral, dorsomedial, "centre median," and a portion of lateral nucleus, the ventromedial part of pulvinar and the habenula. It crossed the ventricle to invade periventricular gray matter and at some levels a narrow strip of dorsomedial and "centre median" nuclei of the right thalamus. The left mammillothalamic tract, left fasciculus retroflexus and the posterior commissure were interrupted by tumour. At no point was the hypothalamus invaded (figs. 2 and 5).

DISCUSSION.

(1) *Summary of cases.*—It is apparent from the microscopical study of the serial sections of Cases 1 and 2, that the areas involved in both instances consist essentially of (1) the periventricular gray system and the small medially-placed nuclei; (2) the dorsomedial nucleus; and (3) the "centre median" nucleus on both sides of the mid-line. The actual boundaries of the tumours, of course, did not coincide exactly with nuclear limits, but the portions of anterior and ventral nuclei and pulvinar which were bilaterally involved in both cases were so small that they may justifiably be omitted from the discussion. Furthermore, bilateral injury to the pulvinar occurred in the control case without the symptom of hypersomnolence.

It is important and interesting to note that the hypothalamus was to a considerable extent uninjured in the first two cases. The nucleus paraventricularis was involved in both, and the rostral portion of the n. supraopticus, the n. tuberis lateralis, and the dorsal part of the mammillary and tubero-mammillary nuclei were destroyed unilaterally in Case 2. Finally, the termination of the tumour within the diencephalon in the cases with hypersomnolence as compared to its extension into the midbrain in Case 3 deserves mention.

(2) *The problem of a sleep centre.*—As Troemner [2] has pointed out the three great questions concerning sleep are (1) the nature of sleep; (2) the question of the existence of a sleep centre; and (3) the location of such a centre if it exists. Leaving aside the other two questions for a moment the possibilities of the existence of an area in the central nervous system controlling the sleep rhythm may be considered. At

first glance the association of hypersomnolence with a relatively small diencephalic or mesencephalic lesion would seem to be strong evidence for such a centre. There are several arguments against such a conclution, however. First, the entire theory of extreme localization of cerebral function has been to some extent unsettled by recent work. Secondly, there is still no conclusive proof of the existence of strictly localized centres in the diencephalon for other processes which are at least approximately comparable to sleep—vascular control, respiratory control, water metabolism, or temperature control. While general areas which are apparently essential to the maintenance of these functions are known, the assignment of any one function to a particular nuclear mass is not supported by the evidence at hand. Finally, and not the least in importance, there remains the fact that postulation of a sleep centre in any one small area leaves unexplained the hypersomnolence associated with lesions in other positions.

(3) *Structure and connections of the areas involved in the reported cases.*—If no sleep or waking centre may be postulated, what explanation can be offered to explain the clinical and experimental data dealing with the problem? In an attempt to attack this question from another angle the physiology and anatomy of the areas involved in Cases 1 and 2 may be reviewed. These areas it will be remembered were principally (i) the periventricular system and the centrally placed nuclei; (ii) the "centre median" nucleus; and (iii) the dorsomedial nucleus.

(i) *The periventricular system.* Clark [43] presents concisely the phylogenetic knowledge of this structure. "In all vertebrates, the dorsal part of the diencephalon and the hypothalamus are linked together by a strand of cells and fibres which form what may be called the periventricular system. In the cyclostome brain this primitive connecting link is apparent as a narrow band lying vertically in the lateral wall of the third ventricle and connecting the habenula with the hypothalamus. Through this periventricular system the somatic correlation centres of the diencephalon are brought into functional relation with the visceral correlation centres." Similarly Rioch [53] noted in the cat and dog that the fibres of the periventricular system connect the nuclei of the medial preoptic areas and hypothalmus with the nuclei of the medial thalamic group, and Huber and Crosby [54] arrived at the same conclusion.

The mid-line nuclei, while probably playing a less important role in man, have been shown definitely in many lower forms (Gurdjian [55], Vogt [56], Clark [43], Rioch [53]) to function not only as commissural nuclei, but in connecting the dorsal and central thalamic centres through the periventricular system.

(ii) *The centre median nucleus.* On the basis of comparative anatomical studies Clark believed the "centre median" nucleus functions as a connecting and correlating mechanism for other thalamic elements. Rioch [57] has presented evidence of a similar character which suggests that this nucleus represents the elaboration of an interstitial group of cells and belongs neither to the medial nor to the ventral group in a strict sense. Finally, Clark and Boggon [58] have shown experimentally (by degeneration studies) that the "centre median" nucleus is connected by short tracts with the surrounding thalamic nuclei and the periventricular system.

(iii) *The dorsomedial nucleus.* It seems possible that this nucleu is not present, or at least not important, in submammalian forms, and Clark has pointed out that its development in the mammals parallels the increasing size and complexity of the forebrain. This is quite in keeping with the good evidence which he has presented that the dorsomedial nucleus is closely connected with the frontal cortex by both afferent and efferent fibres. It is also known to be linked with the other thalamic nuclei, with the striate body, and particularly with the periventricular gray system.

Conclusions regarding the localization of the sleep mechanism. From this brief review of the structure and connections of the dorsomedial and "centre median" nuclei and the periventricular system it is safe to assume that these structures serve as important correlating mechanisms and connecting links between the cortex and thalamus on the one hand and hypothalamus on the other. Furthermore, it has been shown by Beattie, Brow and Long [34, 59, 60] that there are doubtless connections between the hypothalamus and mesencephalon and possibly pons and medulla.

When we consider then the present anatomical and physiological knowledge of the areas involved in the cases showing hypersomnolence which were studied, and the accumulated evidence of other similar studies, it seems probable that the sleep-rhythm is controlled by a relatively wide area (perhaps located in the medial portion of the thalamus) acting as a correlating centre for many cortical, endocrine and exogenous stimuli, and closely bound up with a cortico-thalamico-periventricular-hypothalamico-mesencephalic chain. Since the lesions which have been known to be associated with hypersomnolence have all been located somewhere in this chain of closely connected structures it seems reasonable to believe that the interruption of afferent or efferent impulses to such a central mechanism may also cause disturbance of sleep. From our present conception of its structure it is much easier to regard the gray matter surrounding the third ventricle, or about the rostral end of the aqueduct, for example, as transmitting important afferent or efferent impulses concerned with sleep, than as a static centre controlling such a complex function. The direction of the nerve impulses in such a chain, its relation to the central part of the autonomic system, why its interruption should seem to cause hyposomnolence, rather than insomnia, whether its destruction cuts off inhibitory or stimulatory impulses, whether this chain represents part of only one of two balanced mechanisms: all these remain problems for future solution. For the present, however, the conception of the central control of the sleep-wake rhythm as a rather diffuse correlation mechanism which is dependent for its normal function upon the integrity of a thalamico-periventricular-hypothalamico-mesencephalic chain of neurones, seems best to explain our clinical, experimental and physiological data.

There remains the consideration of Case 3. Here the lesion involved all of the areas destroyed in the first two cases, but almost entirely unilaterally. While the tumour did fill most of the third ventricle and invaded the periventricular gray matter and medial portion of the opposite side in places, it penetrated to a depth of only 1 to 2 mm., except in its caudal extremity which damaged the right pulvinar slightly more extensively. In a careful comparison with the other cases the most logical explanation of the absence of hypersomnolence in this instance seems to be the unilateral position of the tumour.

The evidence relating to this point is somewhat conflicting. Almost all of the carefully studied cases of tumour associated with hypersomnolence produced bilateral disturbances. Spiegel and Inaba could produce hypersomnolence in animals only by bilateral thalamic lesions. On the other hand, Hechst has reported the occurrence of excessive sleep in a patient who was found at autopsy to have a tumour involving only one side of the diencephalon. There is as yet no available explanation of this contradiction, but in the cases of this series bilaterality seemed a prerequisite to the production of hypersomnolence.

SUMMARY.

(1) A survey of the literature dealing with lesions of the interbrain associated with hypersomnolence shows: (i) The evidence favouring various localizations of the sleep mechanism in the diencephalon is inconclusive and not entirely satisfactory. (ii) The relatively small number of careful clinico-pathological and experimental studies suggest

that hypersomnolence may be caused by lesions in: (*a*) the infundibular region; (*b*), the periventricular gray matter; (*c*) the region about the cephalic end of the aqueduct; (*d*) the thalamus (if involved laterally).

(2) A careful clinico-pathological study of three cases of relatively small tumour of the diencephalon, two associated with marked hypersomnolence, and one showing no sleep disturbance, suggests that in these cases bilateral damage to (1) the dorsomedial nucleus of the thalamus, (2) the "centre median" thalamic nucleus, and (3) the periventricular system and mid-line nuclei, was responsible for the alteration of the sleep rhythm.

(3) On the basis of the cases studied, the present anatomical and physiological knowledge of the diencephalon and the accumulated evidence in the literature, it is suggested that disturbances of sleep result from lesions of a rather diffuse central correlating mechanism, which may lie in the medial thalamic nuclei, or from the interruption of a thalamico-periventricular-hypothalamico-mesencephalic chain of neurones conducting impulses to or from such a mechanism.

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THE CEREBRAL BLOOD FLOW DURING SLEEP IN MAN.[1]

BY F. A. GIBBS, E. L. GIBBS AND W. G. LENNOX.

That sleep is produced by changes in cerebral blood flow is a theory which in past years has had wide support. Mosso [1], in 1881, believed there was cerebral anæmia during sleep because of observations made with a tambour placed over the skull defect of a patient. The anæmic theory of sleep has been supported by various physiologists, including Leonard Hill, who wrote "there can be no doubt that sleep or lethargy is associated with cerebral anæmia" [2]. Others have believed that sleep was caused by cerebral congestion. One of the latest contributions is that of Stevenson, Christensen and Wortis [3]. These authors observed increase in intracranial pressure (registered by means of a tambour placed over a defect in the skull) which they interpreted as evidence of fatigue of the sympathetic centre controlling the tone of cerebral vessels. This resulted, they suggested, in dilatation of the cerebral vessels, giving the increase in pressure and a pulling apart of the neurons with interruption of nervous activity.

Although the theory of a vascular explanation of sleep is not emphasized to-day, it is still listed as a possible cause [4] and no direct evidence has been brought forward to disprove it. This, of course, is because observations of cerebral blood flow in man have been indirect, deductions being drawn from changes in intracranial pressure or changes in systemic blood-pressure or in the blood-flow elsewhere in the body. By means of a method recently devised we have found it possible to obtain direct evidence of cerebral blood-flow with reference to sleep.

Records were made of the changes occurring in the blood-flow through an internal jugular vein of anæsthetized patients. The instrument used was a needle flow recorder of a type which one of us has previously described [5]. It consists essentially of a stilet with an electrically heated tip. This stilet is inserted through a hollow needle into the lumen of an internal jugular vein. A constant electric current is applied to the tip of the stilet sufficient to heat it to a temperature slightly higher than that of the blood. As the blood flows past the heated tip it is cooled. When the blood flows more rapidly the tip becomes cooler, and when the blood flows more slowly the tip becomes warmer. The temperature of the tip is measured by means of thermo-junctions in series with a galvanometer. In order that a change in body temperature should not be misinterpreted as a change in flow, the cold junction is mounted on the stilet behind the hot junction; it then becomes possible to measure not the absolute temperature of the tip, but the difference in temperature between the heated tip and the body of the stilet. This difference in temperature varies only slightly with changes in body temperature, but greatly with changes in blood-flow.

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The instrument records changes in the velocity of the surrounding stream. If the cross section area of the stream remains constant, changes in velocity may be interpreted as changes in volume flow. We punctured the internal jugular vein close to its point of exit from the skull, a situation where fluctuations in calibre would not be expected to occur, for where the vessel pierces the skull it has an essentially rigid wall. We believe, therefore, that any observed changes in velocity can be interpreted as changes in volume flow, and where no such changes occurred the volume flow remained constant.

In our experiments the patient lay quietly on a table. Records of the blood-flow and of respiration were taken continuously for a period of from one to two hours. In four instances records were obtained covering periods in which the subjects (epileptic patients who had no disorder of sleep) went to sleep. In no case was there evidence of a significant change in cerebral blood flow either when the patient fell asleep or when he awoke. During calm sleep the cerebral blood flow tended to fall gradually, but this seemed related to a decrease in restlessness and not to sleep *per se.*

A typical record is shown in fig. 1. The changes in blood flow which did occur were probably passive responses to changes in systemic arterial pressure. Certainly, the period of sleep was not accompanied by greater fluctuations in flow than occurred in the control-waking periods.

One of the patients studied had narcolepsy and a history of cataplectic attacks. The record shown in fig. 2 was obtained during one of his characteristic sleep attacks. The general level of the cerebral blood-flow was not influenced by the occurrence of this period of sleep.

These observations indicate that the impairment of consciousness

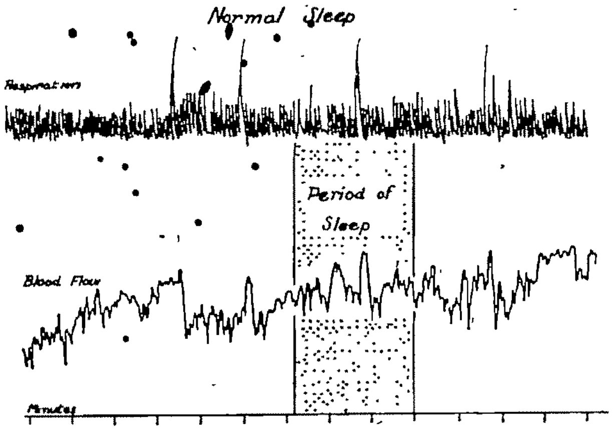

FIG. 1.—The cerebral blood flow during normal sleep. The tracing at the top represents respiratory movements of the chest; the one in the middle, alterations in blood flow in an internal jugular vein; the line at the bottom shows time in minutes. The approximate period of sleep is shown by the dotted area. In this record, the full sensitivity of the string flow recorder was being utilized and minor fluctuations in flow give the record its somewhat toothed appearance.

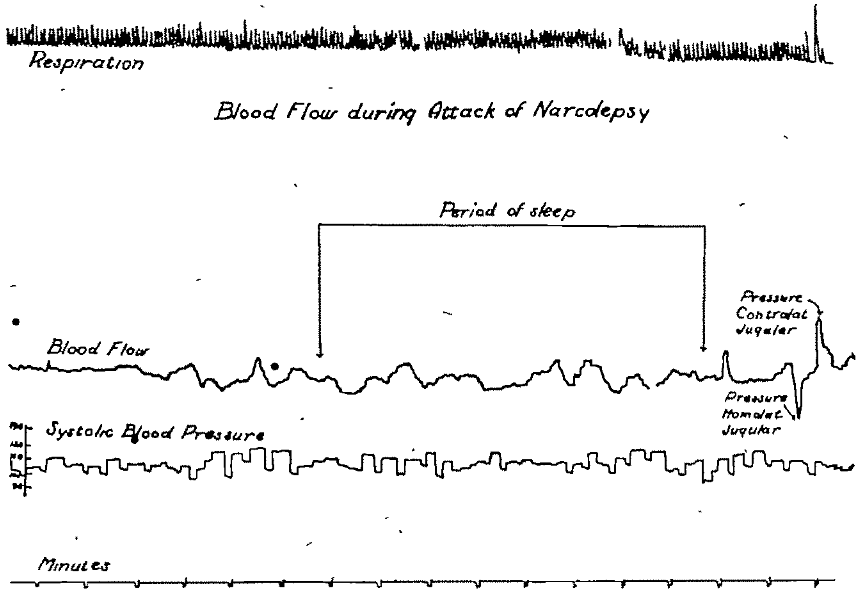

FIG. 2.—The blood flow during a period of sleep in a patient with narcolepsy. Tracings as in fig. 1 except that brachial blood pressure is recorded below the record of the blood flow. At the end of the period of observation the apparatus was tested by light pressure applied over the homolateral jugular vein below the needle (marked Pressure Homolat. Jugular) and then over the contralateral jugular vein (marked Pressure Contralat. Jugular).

which occurs in sleep is not due to a change in the total cerebral blood flow. We found this to be true also in regard to various other types of unconsciousness, notably in petit mal seizures [6] and in syncope from carotid sinus stimulation when no fall in blood-pressure occurred [7] On the other hand, unconsciousness which is associated with orthostatic syncope or with carotid sinus stimulation in which there is a preliminary fall of blood-pressure, is preceded by a sudden and pronounced decrease in cerebral blood flow as measured both by the blood flow recorder and by analysis of the oxygen content of blood from the internal jugular vein [7]. That the flow in itself is not the determining factor is shown by the fact that pronounced diminution of flow can be produced by such procedures as quick change in posture or hyperpnœa [8] without inducing sleep or alteration of consciousness. In unconsciousness produced by the breathing of nitrogen, the cerebral blood flow is increased [8].

A vasoconstriction in a small area of the brain would not have been detected by our instrument. It is possible that circulatory changes, confined to some small portion of the brain principally concerned with sleep, might induce sleep. That the " sleep centre " should be activated by a localized vasoconstriction would appear, however, to be a somewhat elaborate hypothesis for which there is, at present, no direct evidence.

The older observations by means of a tambour deserve some explanation. By the more exact means of observing the pressure of the cerebrospinal fluid, we have confirmed the tambour observations of Stevenson and others that an increase in intracranial pressure takes place when the subject is falling asleep. This increase is, however, slight, amounting to only 20 or 30 mm. of spinal fluid. Probably this increase is not due to an exhaustion of cerebral vasomotor nerve centres but to an increase in venous pressure, or else to a decrease in the respiratory movements and a consequent slight accumulation of carbon dioxide in the blood which enlarges the vascular bed, without overbalancing a coincident slight fall in blood-pressure, and without altering the cerebral blood flow.

Available information does not yet suffice to explain the mechanism of sleep, but the work of Pavlov with conditioned reflexes and internal inhibitions and that of Hess with stimulation experiments suggest that the mechanism is an essentially nervous one. In any case, we feel that the data presented here should form a *requiescat in pace* for a vascular theory that has too long haunted textbooks and neurological literature.

CONCLUSION.

Observations of the cerebral blood flow in man have been made by means of a thermo-electric blood flow recorder inserted into an internal jugular vein. The onset and termination of sleep in subjects without sleep disorder and in one patient with narcolepsy were not accompanied by a significant change in the flow of blood through the brain.

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ON THE "SYNDROME OF THE PREMOTOR CORTEX" (FULTON) AND THE DEFINITION OF THE TERMS "PREMOTOR" AND "MOTOR": WITH A CONSIDERATION OF JACKSON'S VIEWS ON THE CORTICAL REPRESENTATION OF MOVEMENTS.

BY F. M. R. WALSHE.

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I.—INTRODUCTION.

A DEVELOPMENT of recent clinical and experimental studies of the "grasping" phenomena seen in association with certain lesions of the frontal lobes is the formulation by Fulton and his collaborators [10, 13, 19, 20] of a "syndrome of the premotor cortex."

They believe that both in man and in apes a characteristic group of motor disorders meriting this title is to be observed.

The evidence submitted in support of this hypothesis is mainly experimental, and consists in observations made upon apes after circumscribed cortical ablations, but it has recently been supplemented by a clinical case of glioma of the frontal lobe which, they believe, confirms the conclusions reached from experiment and warrants their application to man.

In considering the investigations which have led to the description of this syndrome, it is essential to understand the nomenclature employed by the authors. By the term "motor area" they understand that part of the precentral convolution adjacent to the fissure of Rolando in which are found the giant cells of Betz. This corresponds approximately with Campbell's "precentral area," with Brodmann's "area 4," or with Economo's "area giganto-pyramidalis F A γ" [3, 7, 9].

The "premotor area" lies immediately anterior to the above. It corresponds with Campbell's "intermediate precentral area," with Brodmann's "area 6," and with Economo's "area frontalis agranularis, F B," together with the anterior and ventral part of his area F A.

Now it must be emphasized that the term "motor" or "excitable" cortex is based upon physiological grounds, and denotes the possession by the region so named of certain physiological properties. It implies nothing of the cellular structure of the region in question. This has been generally understood both by histologists and by experimental physiologists.

Thus Brodmann [3] says that his areas 4 and 6 together correspond with the motor cortex. Economo expresses a similar view, and it has been only by Campbell [7] that any suggestion has been made that his precentral area is co-terminous with the motor cortex properly so-called.

But in the papers we are to consider this view of Campbell's has been adopted, and in describing the two areas in question histological and physiological terms have been used as though interchangeable, though it is nowhere explicitly stated that any departure from the customary sense of the term "motor cortex" has been made. Considerable confusion has been created thereby, but for our present purposes we will use the words "motor" and "premotor" in the senses employed by Fulton and his collaborators, considering finally the influence this usage has upon the evaluation of their conclusions.

As Fulton [12] points out, the notion that the region immediately anterior to the motor cortex may have important functions in the synthesis of voluntary movements is no new one. Jackson placed his "highest level" of cortical function in the "præfrontal region," and it was perhaps natural for Campbell, as a histologist, to wish to give it "a local habitation and a name" in the intermediate precentral area he had delimited. Campbell [7] further drew attention to the origin of the fronto-pontine tract in this region and suggested that the latter and the cortical region from which it took origin might represent part of

Jackson's "highest level," the precentral area corresponding to the "middle level." But, as we shall see, so complete an identification of a cyto-architectonic field with a physiological entity is not justified either on histological or upon physiological grounds.

In 1909, Bergmark [1] pointed out that occasionally hemiparesis of cortical origin is unaccompanied by spasticity—unlike the common hemiplegia of capsular origin, while in 1910 the present writer [24] drew attention to various clinical and experimental observations which raised the question as to whether the spasticity accompanying some cerebral paralyses might not possibly be a consequence of a negative lesion of a second descending pathway; namely, the fronto-pontine tract, but no conclusions were drawn.

Again, the idea of "eupraxic centres" lying anterior to the true motor cortex is an old one, such a centre being one wherein "movements are combined ideationally, to be innervated in the sensomotorium (Wilson [26])." It finds a lucid exposition very relevant to our present subject in Wilson's paper published in this Journal: "A Contribution to the Study of Apraxia."

More recent studies of the "grasping phenomena" have again brought to the fore this question of the rôle of the frontal lobe in movement and in posture, and the series of papers by Fulton and his collaborators, to be considered, represents an attempt to throw light upon it.

It is the purpose of the present paper to review the findings and conclusions of these observers, and to consider the probable nature of the cortical representation of movements. We shall also have to consider what may properly be understood by the term "motor cortex."

But before we begin, a little retrospect may be permitted. The past quarter of a century has seen the identification of a number of newly isolated syndromes correlated, on evidence of variable quality, with local lesions in regions of the brain previously little considered by clinical neurologists. Almost invariably we find that, interest once aroused in some particular region of the brain in this way, syndromes localized in it have freely multiplied and functions have been lavishly showered upon it. The corpus striatum and, more recently, the hypothalamus provide cases in point. Outside the neuraxis the sympathetic system also affords an example of the kind.

Frequently much of this new work fails to stand the test of time and the labours of the student in assessing it all are considerable.

The lesson should be of value to us, and in approaching a region of the brain now becoming a focus of attention, namely, the "premotor" region of the cerebral cortex, we shall do well to be cautious in accepting new attributions to it—either of symptoms or of functions—more especially if this should involve removing them from regions their association with which has been firmly established by earlier work.

II.—THE CLINICO-PATHOLOGICAL EVIDENCE FOR THE SO-CALLED PREMOTOR SYNDROME OF FULTON IN MAN.

The direct evidence submitted by Fulton and his co-workers consists so far in but a single case [20]. The lesion was a glioma of the frontal lobe, and hence the syndrome developed gradually—the component signs appearing in what they believe to be a characteristic and pathognomonic sequence. These signs, in order of their appearance, are as follows: (i) Gradually increasing awkwardness in an extremity, affecting more particularly highly integrated digital movements, such as those involved in sewing, piano playing, buttoning a shirt, and without impairment of gross movements; (ii) early appearance of spasticity and increase of tendon-jerks; (iii) "forced grasping"; (iv) late appearance of weakness of grasp and of other "gross movements"; and (v) vasomotor disturbances of the affected parts.

Jacksonian attacks may or may not appear, and the authors believe that a careful examination of the sequence of events will allow of the recognition of the premotor syndrome even before the development of "forced grasping."

They do not record any special clinical studies of a syndrome of the true motor cortex, but they believe that when this develops progressively its signs will be as follows: (i) Generalized "weakness" of the extremity, especially of the grasp, appears precociously; (ii) spasticity if present at all appears late; and (iii) there is no forced grasping. Acute lesions of this region, on the other hand, produce flaccid paralysis and depression of reflexes.

The attribution of the first of the two syndromes summarized above to an exclusively premotor lesion is not one that can be readily accepted as it stands, for in respect of all but its third component, namely, "forced grasping," it represents a sequence of events and signs common to every case of progressive hemiplegia. In particular, the initial loss of isolated and skilled movements of the fingers, and—with the deepening of this loss—the spread of impairment of movement to include larger and simpler movements and those of the proximal segments of the limb, illustrate that "compound order of dissolution" described by Jackson [17] as so characteristic of hemiplegia as ordinarily seen in man. Nor is this transfer of hemiplegia from lesions of the motor area and the pyramidal system to lesions involving only the premotor area and an "extra-pyramidal motor system," rendered more convincing by the summary given of the syndrome of the true motor cortex and the pyramidal system. This does not call up in the clinical observer's mind anything with which he is familiar. We are told that characteristic of this syndrome is not loss of skilled movements of the fingers, but rather a "generalized weakness" of the limb; a loss of power rather than a loss of purposive movements. Since this conception of "weakness" as typical of motor area and pyramidal lesions is strongly emphasized by Fulton and his collaborators and placed in contrast to loss of purposive movements, it must be submitted to some examination.

It seems that we have here a false antithesis between "weakness" on the one hand, and impairment or loss of movements on the other. For example, we find (Jacobsen [18]) that after a motor cortex ablation the affected limb is said to have recovered "motor power," although some hand and finger movements are permanently lost. No such distinction between "power" and "movements" can be drawn. A limb can do nought else than move, and the expression "loss of power" can have no other meaning than "loss of movements."

Further, in descriptions (Fulton and Viets [13]) of the "weakness" associated with motor cortex lesions, we read of paralysis of "muscles" or of a "a specific muscle group" as though muscles and not movements were represented in the cortex. Indeed, it is clear that this is the category in which the writers are thinking, though no sound hypothesis of cortical motor functions can be built upon such a basis. This antithesis between "weakness" and "loss of movements" has no foundation in reality, but seems forced upon the writers by the exigencies of an hypothesis which requires that there shall be two kinds of hemiplegia, "motor" and "premotor." As to the nature of the paralyses following cerebral lesions, Jackson expressed the facts clearly as follows: "I would point out that loss of some movements of the whole of a part, with persistence of some other movements of the whole of that part, is an exceedingly common thing. Take the case of an imperfect paralysis of an arm in ordinary hemiplegia, or after an epileptiform seizure. To say that the arm is 'weak' is misleading. The patient has lost some movements of the whole of the limb, and yet retains other movements of the whole of the limb. Often enough there is loss of some of the most 'delicate' movements, with, at the same time, the retention of many 'coarser' movements. Unable to button his shirt, the patient may be able to grasp strongly, or to strike a heavy blow" [17].

Of the innumerable different movements of which the human hand and arm are capable, some are relatively simple and both early and easily learned. Others are more complex, especially those employing the digits, and much practice goes to their perfecting. Such distinction as we may wish to make between these two extremes is best expressed by Jackson's antithesis, "automatic" and "voluntary," or "general" and "special" respectively. But these are distinctions of degree and not of kind, and in drawing them we are neither required to, nor justified in, postulating qualitatively or topographically distinct cortical representations for the two extremes.

There are *many degrees* of hemiplegia, but only *one kind*, and the expression "loss of power," or "paralysis of muscles," is not applicable to it. Nor may we invoke the appearance of spasticity as a sign necessarily differentiating the premotor syndrome (if there be one) from the motor syndrome, since the rate of development of the lesion, and its progressive or stationary character, are factors which enter largely into the matter.

In this case, therefore, the "forced grasping" is the only component sign of the syndrome which may be confidently ascribed to involvement of the premotor region. The hemiplegia must be assumed to be a consequence of interference with the functions of the motor cortex and its projection system, of which it is a typical example, unless it can be proved that the lesion was in fact wholly confined to the premotor region and was incapable of provoking "neighbourhood symptoms" in the contiguous motor region.

This cannot be proved, for the lesion was a cystic astrocytoma which "pointed" in the frontal cortex just anterior to the ascending frontal convolution. As is well known, it is quite impossible with the naked eye, or in the absence of a minute histological examination of the hemisphere, to determine the limits of an infiltrating growth of this nature. Its margins are invisible, and its extent always greater than can be seen macroscopically. The mass removed at operation was 22 c.c. in bulk, and we may not assume that it comprehended the entire tumour substance. We cannot know to what degree the motor cortex was infiltrated by growth, or its functions disturbed by œdema or reactionary changes. In short, the case does not provide material from which Fulton's deductions can be drawn.[1]

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[1] Twenty-five years ago, Horsley [16] reported the results of an isolated ablation of the arm area of the motor cortex in the human subject. Referring in his paper to other cases on record

In his most recent paper [10], Fulton uses the term "tonic innervation" as a synonym for "syndrome of the premotor cortex," and states that forced grasping never occurs as an isolated symptom, but always associated with the other components of the syndrome enumerated above. It is not possible to accept these statements. Tonic innervation, a term first employed by Wilson and Walshe [27], was used to designate tonic grasping and this alone, and it was never associated by these writers with the hemiparesis which accompanied it in the cases recorded in their paper. Subsequently, Walshe and Robertson [25] have used the term as applying only to the proprioceptive tonic grasping reflex, isolated by them from the complex phenomenon now generally known as "forced grasping." This reflex reaction does occur from time to time in man in the absence of any paresis, change in the tendon jerks or spasticity; that is, without any of the other components of Fulton's syndrome, and one such case is reported by Walshe and Robertson in the paper referred to, and others have since come under the observation of the present writer. There can, therefore, be no justification whatever for using the term "tonic innervation" as synonymous with Fulton's "syndrome of the premotor cortex." To do so is to plunge the nomenclature into unnecessary confusion, and, in so far as reflex proprioceptive grasping may occur without the other components of this syndrome, it is, of course, inaccurate.

In the case of the human subject, therefore, the evidence adduced does not support the occurrence of such a syndrome of the premotor cortex as has been described by Fulton and his collaborators. This is not to say that there are no motor syndromes characteristic of lesions in the frontal lobe anterior to the true motor cortex. What evidence there may be for frontal motor syndromes will be considered subsequently.

III.—THE EXPERIMENTAL DIFFERENTIATION OF "PREMOTOR" AND "MOTOR" SYNDROMES.

It is indisputable that in this matter the experimentalist can command opportunities denied to the clinical observer, but the latter retains the advantage of observing human material and has not to draw inferences from ape to man. Again, it is only rarely (as in Horsley's case of cortical ablation [16]) that a therapeutic intervention in man

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from which conclusions had been drawn as to the functions of this region of the cortex, he wrote:—"With the utmost respect for the opinion of the many distinguished writers on this subject who have published instances of lesions in this region, I venture to object to evidence derived from cases of extensive tumour as scientifically not valid for this purpose."

fulfils the conditions of a planned animal experiment. The manner of development of a disease process in man differs, also, from that of the experimental lesion. In other words, in comparing experimental lesions in animals with the lesions of disease in man, we see that neither the material nor the event is quite the same. In this way the drawing of valid inferences is sometimes rendered difficult.

The series of experiments we are to consider illustrates these points in many ways. Thus, the sequence of cortical ablations in some of the combined motor and premotor experiments was carried out so rapidly that the motor state of an affected limb had not reached equilibrium before it was further modified by the supervention of a second lesion in another cortical region. Thus, however precise the lesions, the apportionment of the final motor state between them has something of a speculative character. Again, ablations of the premotor cortex are carried out on the very threshold of the contiguous precentral cortex, and it would be contrary to experience if transient "neighbourhood symptoms" were not produced to complicate the picture. It is essential, therefore, to differentiate carefully between immediate and transient disorders of function, and later developing and more persisting disorders. That such transient "neighbourhood symptoms" ensue after surgical interventions involving the cerebral hemisphere in man is a commonplace, and even in these experimental procedures they are found to occur. Thus Fulton and Kennard ([12], experiment 7, p. 193) found a transient paresis of an arm after ablation of the leg area of the motor cortex.

Again, it is somewhat hazardous to compare the "immediate" spasticity of brief duration that may follow an ablation of the premotor cortex with the more gradually developing residual spasticity of hemiplegia in the human subject.

Although there is nothing in these considerations not perfectly familar to the clinical neurologist who is constantly seeing them exemplified, yet it may be useful to recall their importance to him when he comes to assess the bearing of experimental lesions of the brain upon the elucidation of the symptoms of lesions in man.

Fulton and his collaborators summarize their observations and draw their conclusions as follows: (i) Lesions restricted to *the motor area* give rise to flaccid paralysis. The return of "motor power" and of normal posture is complete except for the "muscles" of the digits. In the chimpanzee a Babinski plantar response ensues. Spasticity never occurs. (ii) Lesions restricted to *the premotor area* produce as their primary symptom a disturbance of skilled, acquired movements. Animals trained to carry out special movements of this order suffer impairment of "the capacity to execute" them. On the other hand, "gross power" is not affected and grasp remains good even when fine movements are impaired. Spasticity and increase of tendon-jerks and "forced grasping" are also present. Some vasomotor changes may appear in the affected limbs. From these observations the following conclusions are reached: (i) The premotor area is the chief cortical representation of the extrapyramidal motor system and subserves "the integration of complex volitional movements and postural adjustments." (ii) Within certain limits (nowhere defined) the pyramidal system is able to compensate for loss of the premotor cortex, and, in its turn, the premotor system is able to mediate certain voluntary movements in the absence of the pyramidal system.

It is noteworthy that these conclusions contain no statement as to the functions now assigned to the motor cortex and pyramidal system, since, as we shall see, those attributed to them by Leyton and Sherrington are boldly transferred to the premotor cortex and an extrapyramidal system.

Our task of assessing the experimental evidence in favour of the occurrence of two distinct syndromes, motor and premotor, would be simple could we assume that the summary just given adequately generalized the facts of observation as recorded by Fulton and his collaborators in their protocols, or justified their conclusions. But we cannot do so, for a study of these protocols reveals wide divergences on essential points between observation and summary thereof. We must, therefore, make our own analysis of the facts and draw our own conclusions, and in doing this it will be of value to describe—as standards of comparison—the results of motor cortex ablation in man as reported by Horsley, and in the chimpanzee as reported by Leyton and Sherrington [22].

(i) *Ablation of the True Motor Cortex in Man and Apes.*

The human subject (Horsley [16]).—The patient was a youth who suffered from violent athetotic movements of the right arm. When the limb was quiet his movements are described as being normal and powerful. The reflexes were normal. The arm area of the motor cortex was carefully delimited by stimulation in the usual way, and it was then carefully excised with minimal disturbance to the blood-vessels. The excised gyrus was examined histologically by Holmes and identified as of true motor cortex structure. The immediate results were disappearance of athetosis and total loss of voluntary power in the limb (right arm). During the ensuing weeks the return of voluntary power followed the usual course. At the end of the third week abduction and adduction of the shoulder; next, flexion of the elbow, then extension of the elbow and flexion of the wrist. Digital movements returned later; first, flexion of the thumb, then extension of this and the other digits, the little finger moving not at all. Horsley then observes that "As regards flexion, the complication of hypertonia comes in, because the ordinary hypertonia or contracture affects as usual the most paralysed part, and therefore when the digits are flexed the small fingers curl up into the palm, and the wrist, instead of remaining extended, follows suit." Finally, the hypertonia was most marked in the flexors of the ulnar fingers and remained as a permanent residual state. Fine, isolated movements of the digits never returned. With the sensory defects noted we are not here concerned.

Fortunately for our present purpose this case was the subject of intensive investigation by Head and Holmes during the course of their studies on "Sensory Disturbances from Cerebral Lesions" (this journal, 1911, 34, 102), and their notes record that seven months after the cortical ablation there was "distinct increase of tone in all muscles from the elbow distally. The fore-arm cannot be supinated without the exertion of force continuously applied." Similarly, force was required to bring the fingers and hand into the same line as the forearm. On relaxing this force the hand and fingers slowly went back into flexion again. The left arm jerks were brisker than the right.

At the elbow there was fair power of voluntary flexion but less of extension. Supination was weak and incomplete, pronation stronger and more complete. Flexion of the third and fourth fingers was complete in range, but that of the index very incomplete and feeble. The two radial fingers could be almost fully extended, but the remaining fingers very feebly and incompletely. There was no power of flexion of the thumb, but feeble extension.

Associated movements (symmetrical) were present in the left hand on forceful movements of the right.

There was slight general wasting of the limb.[1]

Leyton and Sherrington's findings on isolated ablation of the arm area *in the chimpanzee* are identical with those recorded above as

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[1] The writer is indebted to the courtesy of Sir Henry Head and Dr. Holmes for the opportunity of studying their notes of this case.

occurring in the human subject. Thus, the immediate result was loss of movements in the limb, maximal for those of the digits and minimal for those of the proximal segments of the limb. The lost and impaired movements of the latter rapidly returned, but the purposive movement of the digits, particularly isolated movements of thumb and index, were at once the most severely impaired and the most imperfectly restored. The original scar was then re-excised at a second operation. At this juncture these observers note that "the tendency to contracture noted before the second operation has become more pronounced. The arm tends to be kept partially flexed at the elbow, and there is some postural over-extension of the metacarpo-phalangeal joints, with some flexion of the phalangeal joints of all the digits except the thumb." In this experiment the state of the tendon-jerks is not noted, but after a "leg area" extirpation it is noted twenty-four hours after operation that the knee-jerk was increased.

We see, therefore, that there are no essential differences between the changes in motility produced in man, and those produced in the chimpanzee, by isolated ablation of the motor cortex.

The observations of Fulton and Kennard [12] are also essentially identical with these, though their summary and conclusions do not indicate the fact. Thus, they found the same initial widespread loss of movement, the rapid return of movements in the proximal segments of the limb, and the same imperfect restoration of skilled digital movements. Hypertonus, also, appears to have made its appearance in the most paralysed parts of the limb. This is clearly indicated by the statement that the affected arm—even when extensively and deeply paralysed—tends to adopt and to maintain a semi-flexed attitude (a criterion accepted by these observers as indicative of hypertonus). In one instance, Jacobsen [18] reports the persistent adoption of this attitude, while after bilateral ablation of the "leg area," Fulton and Keller [11] state that the postural condition of the lower limbs is "entirely similar with respect to reflexes, adduction of the extremities, lateral deviation of the toes and a tendency to pes equinus; it differs only in one respect, namely, in the *degree*[1] of spasticity" from the state of the legs in human cerebral diplegia (Little's disease).

It cannot be maintained, therefore, that persistent flaccidity is a characteristic of paralyses following ablation of the motor cortex.

The depression of the tendon reflexes is but an immediate effect, and they may ultimately become exaggerated (Fulton and Keller, p. 108).[1]

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[1] Italic not in the original.

A further interest is added to these experiments by the fact that a certain number of animals were subjected, before operation, to training in feeding-box problems (Jacobsen [8]). It was found that, after motor cortex ablation, although the animal appeared to retain the habits previously inculcated, yet the imperfect restoration of hand and finger movements proved an obstacle to their efficient motor execution. This observation corresponds with the findings of Leyton and Sherrington, namely, that "the fore-running idea of the action intended was present and as definitely and promptly developed as usual. All the other parts of the motor behaviour in the train of actions coming under observation seemed accurate and unimpeded except for the role, as executant, of the particular limb whose motor cortex was injured . . . raising the question whether the function of part of the cortex ablated in such cases be not indeed infra-mental" (p. 206).

In conclusion, we find that the state of a limb after ablation of its motor cortex representation corresponds closely to Jackson's description cited earlier. The final result is permanent impairment of skilled purposive movements of the hands and fingers, with some hypertonus in the paralysed parts. The generalization that "general weakness," flaccidity and depression of reflexes are the characteristics of motor cortex ablation is seen not to be in accord with the facts, as recorded by Horsley, Leyton and Sherrington, and also by Fulton and his collaborators. The term "general weakness" has no place in a precise analysis of the loss of movements following cerebral lesions. It takes no account of the nature of the loss, nor of the nature of the cortical representation of movements.

Finally, it is noteworthy that this state of affairs, following motor cortex ablation, corresponds in detail with what Fulton believes to be the sequel of ablation of the premotor cortex, with the single exception of the forced grasping that ensues upon the latter.

(ii) *Ablation of the "Premotor" Cortex.*

The results of ablation of the premotor area, unilaterally or bilaterally, alone and in association with ablation either of the frontal (prefrontal) region, or of the true motor cortex, are so paradoxical that their interpretation has so far proved impossible, and their correlation with anything observed in the human subject extremely difficult.

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[1] A single experiment is sometimes reported by Fulton and his collaborators in more than one paper, and the descriptions sometimes differ on essential points. Thus, Fulton and Keller [11] state that after ablation of the leg area in a chimpanzee, the knee-jerk became "hyperactive" on the third day. Kennard and Fulton [19], reporting the same experiment, say that the tendon jerks were depressed for "several days," do not mention that they ever became hyperactive, and state later in the paper that such hyperactivity was not observed.

This is well illustrated in the observations of Richter and Hines [23]. Using the macaque, they find that while purely cortical excisions of the premotor region are without visible effect, deeper ablations in this region going through to the mesial aspect of the hemisphere as far ventrally as the corpus callosum are followed by the transient appearance of "forced grasping" in the crossed limbs. If such a deep ablation be performed bilaterally, bilateral forced grasping ensues and remains permanently, only to disappear immediately if the corpus callosum be divided. On the other hand, if the entire frontal region anterior to the true motor cortex be ablated on one side, a transient and inconstant "forced grasping" may develop on the opposite side, while if this be done bilaterally, forced grasping ensues and is more persisting.

It appears, further, that deep bilateral excision of the premotor region evokes the appearance of "forced grasping" only when the corpus callosum remains intact, disappearing when this is divided. Richter and Hines were concerned solely with forced grasping and do not therefore record any other motor disturbances following their experimental ablations.

Fulton and Kennard did not carry out all these various combinations of cortical and corpus callosum ablation, and their results, in consequence, tend to make the problem of a premotor syndrome appear somewhat simpler than, in all probability, it really is.

In the chimpanzee [12] unilateral ablation of the premotor area is followed immediately by a total flaccid hemiplegia. Within a few days there appears a tendency to the adoption of a semi-flexed attitude in the arm and feeble forced grasping and some resistance to passive movement. The hemiplegia clears rapidly and completely—within a week—and after this time nothing is seen but "a lag in the initiation of voluntary movement." The forced grasping and hypertonus also disappear.

But it appears that there is a permanent defect remaining, for Jacobsen [18], examining a problem-box trained chimpanzee after the fugitive paralysis of a premotor cortex ablation had passed off, noticed that while the animal showed no defect of fine movements or of co-ordination, it nevertheless appeared unable to "organize" the necessary manipulations and had to relearn them. Thus, he says, "although unilateral premotor lesions did not result in residual motor deficits which made the execution of fine adaptive movements difficult, the organization of these movements . . . . was greatly disturbed and necessitated post-operative relearning."

This is an essentially different disorder from that described as following motor cortex ablations, and the neurologist will be struck by its resemblance to the motor disorder known to him as *motor apraxia*. Here is no question of a loss of highly integrated digital movements, which is Fulton's interpretation of the condition, but of the animal's *not knowing how* to set about the necessary movements, and having to relearn them. Apraxia is a phenomenon difficult to investigate in an animal and one with which the experimental physiologist is not familiar. This last point is made clear in Kennard and Watt's paper [21] on the results of division of the corpus callosum. They remark that apraxia is a disorder said by clinicians to follow lesions of this structure in man, and add that apraxia "is at best rather a vague term." Yet Wilson's [26] definition of motor apraxia applies admirably to the disorder described by Jacobsen, namely, "inability to perform certain subjectively purposive movements or movement-complexes, with conservation of motility, of sensation, and of co-ordination."

(iii) *Combined Ablation of the Motor and Premotor Cortex.*

The final, residual effects of this appear to have been fairly constant. The immediate result is a severe hemiplegia and slight "spasticity." Transient and feeble forced grasping appeared on the fourth day. The spasticity gradually diminished and the final result appears to have consisted solely in residual hemiparesis with little spasticity (Fulton and Kennard, experiment 5: Baboon). The impairment of hand and finger movements remained severe. This increased depth of residual paralysis appears to have been the sole permanent effect of the addition of premotor ablation to that of motor area ablation.

In the chimpanzee (experiment 8) the results were essentially similar, but in this case both motor areas had been removed, and the spasticity and forced grasping in the arm affected by the combined ablation appear to have been more severe and a little longer lasting.

In both experiments, the forced grasping developed after a latent period of three or four days.

(iv) *Bilateral Ablation of the Frontal Lobe to the Anterior Border of the Motor Cortex.*

This ablation has a special interest for the neurologist in that it reproduces a picture resembling that not infrequently seen in cases of frontal lobe tumour in man. The animal shows a striking lack of spontaneity, remains motionless for long periods, moves slowly, and when eating continues chewing movements after the morsel has been swallowed (? perseveration). This is bilateral forced grasping, but *no spasticity and no paralysis.* There is nothing to tell us whether or not any dyspraxia was present. This animal passed through a phase of great restlessness. As may be seen in the human subject, the presence of forced grasping is not necessarily accompanied by any spasticity, a finding which does not confirm Fulton's association of these two phenomena as integral components of the premotor syndrome, and suggests that, after all, the appearance of spasticity as a residual symptom requires, and depends upon, a lesion of the motor cortex or of its projection system.

A somewhat similar loss of motor initiative was found by Kennard and Watts [21] to follow division of the corpus callosum alone. No observations of a kind capable of detecting the presence of apraxia appear to have been made in either of the two experiments just referred to.

(v) *Bilateral Ablation of the Premotor Cortex.*

This is the only lesion productive of permanently demonstrable forced grasping, and after this procedure the phenomenon is present bilaterally. This was found both by Richter and Hines and by Fulton and his collaborators.

It may be mentioned in passing that bilateral ablation of both motor and premotor areas produces permanent total paralysis of voluntary movement, spasticity and forced grasping. The condition of the animal is said [12] to be identical with that of the "thalamus animal," but those who are familiar with Magnus's description of this will not be able to recognize any close similarity between the two. The thalamus animal is not, it is true, capable of volitional movements, but as reflex reactions it has a range of motor activities not found in the monkey after the ablation described above.

(vi) *Conclusions.*

Summing up these various observations, it appears that Fulton's generalization that "grave postural and motor disturbances" follow premotor area ablations, scarcely conveys an accurate impression. In macaques unilateral ablation has no visible effect, and in the chimpanzee the fugitive hemiplegia is probably a neighbourhood symptom. Forced grasping in this animal is transient and the sole residual defect is the one we have provisionally identified with motor apraxia. There is no evidence of an essential loss of skilled movements of the digits.

Combined (unilateral) motor and premotor ablations merely produce a more severe degree of hemiplegia than does ablation of the former area alone, together with the appearance of forced grasping. Fulton suggests that the spasticity of residual hemiplegia in man is due to the addition of a lesion of the premotor projection system to a pyramidal lesion, but the recent examination of human pathological material by Davison and Bieber [8] appears to render this view untenable.

Further, considering the obscure and sometimes conflicting statements about hypertonus or "spasticity" which appear in the various papers of Fulton and his collaborators, a doubt must arise in the mind of the clinical neurologist as to what these experimental observers really understood by the term, how they determined its presence or absence, and finally where they expected to find it in a limb of which only the distal part remained partially paralysed.

For their protocols appear to provide clear evidence of the presence of some hypertonus in the affected limbs of their animals after "motor area" ablations, yet they deny its presence. Purely clinical methods of examining the state of tonus were employed in these experiments, and it is probable that some unfamiliarity with clinical criteria accounts for the discrepancy noted between observation and conclusion. It would undoubtedly be advantageous in such experiments for an experienced clinical neurologist to apply the routine methods of investigation ordinarily employed. It is by such means only that sound comparisons between animal and human material can be made.

With the nature of the phenomena somewhat unsuitably grouped together under the title of "forced grasping" it is not proposed to deal in this paper, but we may say that the observations we have been considering do confirm the conclusions set forth by Walshe and Robertson [25], namely, that there are two components in forced grasping: (1) a volitional component (the so-called "groping" and "grasping" movements); and (2) a tonic contraction of the finger flexors when submitted to stretch, a true proprioceptive reflex action. Fulton [10] objects to the use of the term "volitional" in this connection on the ground that *all* possible movements are reflex, but the value of the objection may be judged by the frequency with which the term is employed in their papers by Fulton and his collaborators, even in connection with forced grasping. It is impossible to escape the use of the term, which has a meaning at once clear and generally understood.

We may conclude, therefore, that the sole symptom we may safely attribute to destroying lesions of the "premotor" cortex is forced grasping, and this in turn is conditional upon the integrity of the corpus callosum. All the other symptoms must be ascribed to disturbance of function in the motor cortex and its projection path. That they are all constantly produced by ablation of this area of the cortex confirms this conclusion. Further, it appears probable that apraxia may be a residual effect of premotor cortex ablation.

IV.—THE DEFINITION OF THE "PREMOTOR" AND "MOTOR" AREAS.

In the experimental investigations we have been considering we have seen a tendency to transfer to the "premotor" cortex and its hypothetical "extrapyramidal" projection system functions hitherto accepted as belonging to the true motor cortex and the pyramidal system. If we accept these new views, it is difficult to see what rôle remains for the latter, and Fulton and his collaborators have not formulated any conclusions on the matter. Now the functions of the motor cortex of the physiologist have been clearly formulated by Leyton and Sherrington on the basis of what still remains the most exhaustive and skilled investigation that has been made. They conclude that these functions are "the upbuilding of larger combinations (of movements) varied in character and serviceable for purposes of different and varied kind. The functional properties of this cortex seem specialized to that end. . . The motor cortex appears to be par excellence a synthetic organ for motor acts . . . an organ for synthesis of movements—and of postures—on a vast scale." But, as we have seen, these are precisely the functions now attributed by Fulton to his "premotor" cortex.

Seeking for some explanation of this extreme change of doctrine, we may find it in part in that use of nomenclature to which reference has been made in the introduction. For when Fulton and his collaborators use the term "motor area" they have in mind the area gigantopyramidalis, which they have *assumed* to be co-terminous with the physiologically delimited motor cortex. As a corollary, all that cortical region lying between the anterior limits of Campbell's intermediate precentral area and the area gigantopyramidalis becomes the "premotor area." This last-named area has its own "extrapyramidal" projection system, the pyramidal tract being relegated to the area gigantopyramidalis.

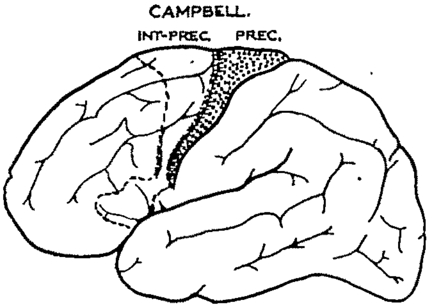
It seems clear that the very existence of a physiologically differentiated premotor cortex, and also that of the syndrome of this cortical area, depend upon the accuracy or otherwise of this identification of a physiological with a cytoarchitectonic entity. If, in fact, the motor area, properly so named, be more extensive than this assumption allows, the premotor area, with its functions and its syndrome, is largely swallowed up by the motor area.

The solution of the question involves a consideration of both anatomical and physiological evidence. Taking the anatomical aspect first we find that *the precentral area* of Campbell (Economo's area FA) is limited posteriorly by the floor of the fissure of Rolando. According to Economo [9], "near the edge of the hemispheric cleft, this formation reaches in the frontal direction beyond the anterior wall of this gyrus (ascending frontal), and even passes over the precentral sulcus as far as the posterior lip of the precentral or the first frontal gyrus. Farther ventrally, its anterior limits shrink rapidly, so that at the level of the superior frontal furrow it is already behind the front lip of the precentral gyrus; at the height of the second frontal furrow it is again behind the middle of the crown of the precentral gyrus. It then falls back rapidly into the floor of the fissure of Rolando at its ventral end."

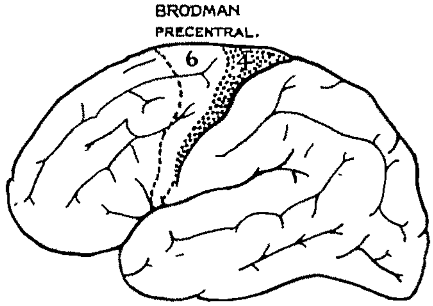
But within this precentral area, and less extensive than it, lies the area in which are found the giant cells of Betz (area gigantopyramidalis, FAγ). Dorsally, the anterior limits of this coincide with those of the precentral area (FA), but ventrally to the first frontal furrow "the anterior limit of FAγ recedes much more rapidly than that of FA; so that at the level of the second frontal gyrus the former has reached the posterior lip of the gyrus (ascending frontal), and has sunk completely into the depths of the posterior wall in the region of the third frontal gyrus. That is to say, in the region of F3 giant cells are to be found only in the deep portion of the posterior wall of the precentral gyrus sunk in the fissure of Rolando" [9]. In short, the giant cells lie massed in the dorsal and caudal parts of area F A. Brodmann's "area 4" appears to coincide with Economo's area F Aγ, and not with the entire area F A.

The intermediate precentral area of Campbell (Economo's area FB. lies immediately frontal to the area just described. It shows a structure similar to it, except that it contains no "giant cells." It stretches "from the sulcus calloso-marginalis on the median surface over the mesial edge of the hemisphere and the entire frontal convexity as far as the opercular area. Its fronto-caudal diameter lessens considerably as we trace the region ventrally, so that, while it covers several broad strips of the great first frontal gyrus at the edge of the cleft, it is reduced to the precentral gyrus alone in the opercular region" (Economo).

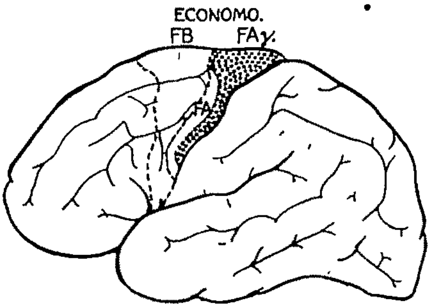
Finally, it may be noted that Brodmann includes his areas 4 and 6 within his "area precentralis," which he correlates with the physiological "motor cortex." Fig. 1 makes these three terminologies clear.



Campbell.—Precentral area = Betz cell area, plus a narrow zone of transition between it and the intermediate precentral area.



Brodmann.—Precentral area = both the above areas. Betz cell area = area 4, and the region anterior to it is area 6. Both together are named precentral area and are thought by Brodmann to correspond to the physiologists' "motor cortex."



Economo.—Area FAγ = Betz cell area. Area FA = entire precentral area, which is of greater extent. FB = area frontalis agranularis. FA and FB together correspond to the "electro-motor zone" of the cortex.

FIG. 1.—Of these three histologists, Campbell alone identifies the area gigantopyramidalis with the motor cortex of the physiologist. Brodmann says: "Auch hier fällt das 'Reizfeld' räumlich fast genau mit meiner Regio precentralis, also den beiden cytoarchitectonischen Feldern 4 und 6 (nicht etwa nur der Area gigantopyramidalis), zusammen."

This somewhat lengthy recapitulation of the different architectonic delimitations of these cortical regions is essential before we come to consider the limits which physiological experiment has placed to the "motor cortex." It is seen that an identification of this region with the area gigantopyramidalis is nowhere made by the physiologist, nor has any histologist except Campbell explicitly made it.

Leyton and Sherrington [22] have shown that the true motor cortex has no sharply defined anterior limit, and have described at great length and in detail the various physiological and individual factors which determine its anterior limits. They write: "It is instructive, therefore, to compare the limits of the motor field as determined by faradization in those anthropoids with his (Campbell's) 'precentral area' determined by cell and fibre lamination. The posterior borders of the two as delimited by these two different methods seem to agree so closely that there can be little doubt that as regards that limit the two fields or areas are the same. In regard to the anterior border, the motor field's boundary seems to lie, especially in its lower two thirds, farther forward than does that of Campbell's precentral area. The anterior boundary, as determined by faradization, is, however, not a sharp one, and its situation seems to vary somewhat from specimen to specimen. As placed by us, it certainly appears to lie for the most part in the intermediate precentral area of Campbell. Opposite the 'arm area' it lies not far behind the anterior boundary of the intermediate precentral area, but opposite the 'leg area' more considerably so. Opposite the 'face area' it lies very much further behind the anterior limit of intermediate precentral area, although in front of anterior limit of the pure precentral area of Campbell. Campbell, in his original description, furnishes a number of arguments in favour of his intermediate precentral type of cortex possessing motorial functions, though differing from the precentral type or motor cortex pure. The gradual shading off of the pure motor field in the anterior direction, as experienced in our observations, and the variability of its anterior edge, as mentioned above when faradized under different experimental conditions, seem to us to lend support to his contention, although the latter was put forward on other evidence" (p. 158).[1]

It is clear, therefore, that the identification of the area gigantopyramidalis, or even of the entire precentral area, with the "motor cortex" of the physiologist is erroneous, since the last-named area includes a considerable extent of the histologically delimited intermediate precentral area.

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[1] Yet another experimental investigator has expressed himself in the same sense. Thus, Rothmann says: "Vor allem ist die mit Riesenpyramidenzellen besetzte Area gigantopyramidalis weder mit dem elektrischreizbaren Rindenfeld noch mit der motorischen Region der Grosshirnrinde noch endlich mit dem Ursprung der corticospinalen Bahn zu identifizieren. Das geht nicht nur aus den Ergebnissen am niederen Affen, sondern auch aus den, vor allem mit Hilfe der Rindenextirpation, beim Anthropoïden und Menschen gemachten Beobachtungen mit Sicherheit hervor." (Über die physiologische Wertung der cortico. spinalen (Pyramiden-) Bahn. *Arch. f. Anat. u. Physiol.*, Physiol. Abteil., 1907, 2-17 Nothing that has since happened requires any modification of the views herein expressed.

Further, it is of interest that these physiological observations afford no ground for thinking that the motor functions of that part of the intermediate precentral area included within the motor cortex (properly so-called) differ in any way from those displayed by the precentral cortex.

Parallel with the assumption that the motor cortex, properly so-called, is identical with the area gigantopyramidalis goes another: namely, that the pyramidal tract arises solely from giant cells within this area.

Some twenty-five years ago, Horsley, in a paper already referred to, gave adequate reasons for rejecting any such assumption. He said "that to include the whole efferent or motor area as determined by excitation we must take two of Campbell's regions, both his intermediate precentral and his precentral areas, although he wishes, apparently, the term "motor" to be restricted to the latter. This suggested restriction of the term "motor," namely, because the giant cells of Betz are to be found only in a certain (the major) portion of the precentral gyrus, cannot be justified, since it would exclude the motor centres for the face, larynx, pharynx and eye muscles, as well as part of the representation of head movements. It also disregards the anatomical rule that an efferent or motor cell varies in size according to the distance the axone has to travel in the central system—for example, the largest pyramids in the precentral gyrus are in the leg area."

But there are other cogent reasons for rejecting this restriction of the pyramidal tract to the axones of giant cells within the Betz cell area. The fact that the cells to which the descriptive term "giant" has been applied lie solely within this area is not a proof that the pyramidal tract arises only within it. The first precise study of its origin is that of Holmes and Page May [15], and while they accept the "giant cell" origin of the pyramidal tract, they accept wide variations in size for these cells, variations which they correlate with differences in the calibre of the cortico-spinal fibres. It is noteworthy that the area of distribution of these cells, in man and in chimpanzee, which they figure in their paper (figs. 7 and 8) is more extensive in an anterior-posterior direction than is seen in the cortical maps of Campbell (*cf.* Plate IX) and of Economo. They remark that this distribution corresponds with the physiologically delimited motor area, and it is apparent that the degree of correspondence between the two is greater in these figures than in those of the other authorities referred to.

Clearly, the statement that the "giant cells" alone give rise to pyramidal fibres has no meaning unless we are agreed as to what constitutes a giant cell. On examination we find that our standards on this point are various, arbitrary and without discoverable physiological value. According to some authorities the standard of identification is purely dimensional, and Brodmann [3] cites several such standards as given by different observers. Economo [9] has yet another standard and states that "all pyramidal cells larger than 60 or 100/25 or $60\,\mu$ are to be considered as giant cells." He is, however, careful to avoid any physiological inferences from what can be no more than a purely descriptive convention, for he states that "axones of other large pyramidal cells in area FA" give rise to pyramidal tract fibres, and he points out that in conformity with a general law in the anterior half of the cortex, the largest cells lie in the dorsal and caudal portions of each histologically differentiated field. Bevan Lewis [2] accepts as giant cells, cells which are of markedly smaller dimensions than those allowed by Economo, and as we have seen Holmes and Page May also accept wide variations in size and indicate the difficulties involved in determining the anterior limits of their distribution. In discussing this question of the cells of origin of the cortico-spinal pathways, Economo and Koskinas in their large work on the cytology of the cerebral cortex express themselves quite emphatically, saying, "es vielleicht doch ein Trugschluss ist, in den man gar leicht verfällt, wenn

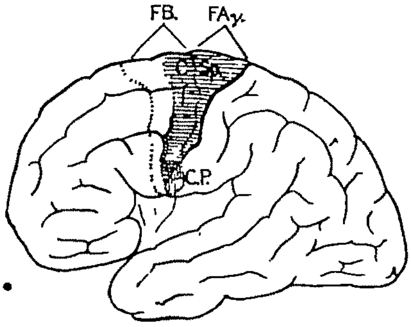

Fig. 2.—(Economo and Koskinas. Figs. 87 and 92). Showing the relation of the origin of the cortico-spinal (C.Sp.) and cortico-pontine (C P.) fibres to areas FAγ and FB. The area of distribution of the pyramidal cells of 3rd and 5th cortical layers from which these pathways arise is cross-hatched.

man im allgemeinen nach der Grosse der Zellen auch ihre Bedeutung und physiologische Dignität schliessen durfen glaubt."

The fact that "giant cells" have been described in the frontal and superior parts of the postcentral convolution by all observers from Betz to Economo, in the same cortical layer as the giant cells of the area præcentralis gigantopyramidalis, is an apt commentary upon this aphorism. The authors illustrate what they believe to be the area of distribution of the cells of origin of these pathways and show that this is not co-terminous with the area gigantopyramidalis (fig. 2).

In short, the "giant cell" is a dimensional and not a physiological entity and we can scarcely blame the histologist if it has come to be regarded as the latter.

Finally, we have the recent investigations of Hoff and Hoff [14] which appear to indicate that the area 6 of Brodmann, Campbell's intermediate precentral area, also furnishes fibres to the pyramidal tract.

In short, the hypothesis that the pyramidal tract derives solely from cells within the area gigantopyramidalis is as unfounded as that which identifies this area with the motor cortex of the physiologist. Both run counter to experimental and histological facts of observation.

The terms "motor" and "premotor" are not interchangeable with the terms "precentral" and "intermediate precentral" (or with "area 4" and "area 6"), and the conception of two sharply differentiated cortical regions, each with its own projection system, and each with widely differing functions, is illusory. The true motor cortex includes much of Fulton's "premotor area" and the pyramidal system arises within all parts of it.

That a fronto-pontine tract arises also somewhere within the more anterior parts of this area is another matter, and the functions of this path remain to be elucidated.

Added to the confusion created by this inexact use of nomenclature is yet another factor making for misunderstanding. As we gaze at any one of the various cortical maps, such as Campbell's, Brodmann's, or that of Economo, we may easily gain from them the impression that the cytoarchitectonic boundaries thereon depicted are as clear-cut, constant and immovable as the field boundaries we may see from an aeroplane, and that we may use them as we would a physiographer's map. They have not this precision nor do their authors claim it for them. They represent simply a composite picture and do not reveal those individual variations and those zones of transition upon which all histologists insist. Moreover, there is a deliberately produced simplification about them, and they represent as though upon the exposed surface of the convolutions regions that are in fact buried in the sulci. This is strikingly the case with the area gigantopyramidalis, as a comparison between Campbell's Plates I and IX will reveal. In its lower half this area is wholly buried in the anterior wall of the fissure of Rolando, and would scarcely appear on the surface in a picture which did not distort the cerebral contours.

The practical bearing of this digression is that while it may seem from a study of the cortical maps to be a simple matter to ablate a portion of the area gigantopyramidalis, leaving the region immediately anterior to it intact, in practice the difficulty of a pure ablation of the area must be almost, if not quite, insurmountable. Yet, this is in fact what a pure motor cortex ablation means in Fulton's hypothesis, though not in his experiments. One has only to study the neurological literature dealing with the interpretation of symptoms to see how frequently an undue preoccupation with pictures, and a failure adequately to consider the organ they so imperfectly represent, has proved adverse to fruitful investigation.

That these various points we have discussed are not merely academic objections without practical bearing upon our subject, but are of the greatest significance, may be seen in a case of so-called "premotor cortex ablation" reported by Bucy and Buchanan [5]. The case was that of a child with a residual spastic hemiplegia, athetosis of the affected arm, and recurrent epileptiform fits. To abolish the athetosis the writers excised that portion of the pre-central convolution which, on faradic stimulation, yielded movements of the affected limb. The area they excised is seen from their diagram to lie wholly within the "motor cortex" of the physiologist, and almost wholly within the precentral convolution, yet because it lies anterior to the area gigantopyramidalis they describe it as a "premotor" ablation, for they regard the area gigantopyramidalis as identical with the physiological "motor cortex."

The case therefore stands on record in the literature as an example of the abolition of athetosis by ablation of the premotor cortex, and as an illustration of the destruction of an irritable focus (in this area) which was discharging disorderly impulses along an extrapyramidal path to the ventral horn cells. Manifestly these conclusions rest upon wholly erroneous premises.

Conversely, if the authors' localization of their lesion in the premotor cortex were correct, forced grasping should have ensued in the affected hand. It did not ensue.

In this discussion we have assumed that the cytological and physiological factors are essentially the same in man and in the anthropoid, and all the evidence indicates that such an assumption is justified, for the histological areas are in all important details the same in each case, and as far as we know the "excitable" area of the cortex is also identical.

V.—GENERAL CONCLUSIONS: THE NATURE OF THE CORTICAL REPRESENTATION OF MOVEMENT.

In the series of papers dealing with a so-called syndrome of the premotor cortex, which we have passed under review, many problems have been raised with which we have not attempted to deal. Such are the nature of the complex of phenomena known as "forced grasping," the bilaterality of cortical representation of movements [6], the excitability of the premotor cortex, the occurrence of vasomotor disturbances and the cytoarchitecture of the premotor area [4].

To have considered all these diverse questions would have unnecessarily confused the three simple problems we set out to discuss; namely, the evidence for the occurrence of a recognizable syndrome of the premotor cortex, the characters of the syndrome of the motor cortex, and the precise meaning to be attached to the terms "motor" and "premotor."

Perhaps the last problem should have been considered first, for if these two terms do not embody precise and consistently employed conceptions, no hypotheses based upon them are likely to be valid. In the event we have found that these two terms have been used in a wholly arbitrary sense, and in so far as the term "motor cortex" is concerned, in a sense essentially different from that understood by all other workers in this subject. We have seen that this term is a physiological one and cannot be used to indicate either the precentral area, nor that part of it known as the area gigantopyramidalis. It includes the entire precentral area and a considerable extent of the intermediate precentral area (Campbell), and the failure to recognize this, although it has been clearly laid down by numerous authorities, has largely vitiated the evidence upon which it has been sought to erect two distinct syndromes, one of the "motor" and the other of a "premotor" area.

An even larger question is raised by the conception of the cortical representation of movements embodied in the papers of Fulton and his collaborators. It is necessary that we should try and define what we may understand by the expression "cortical representation of movements."

Various views on this subject compete for acceptance. On the one hand, we have the view exemplified in the writings of Campbell—and adopted by Fulton and his collaborators—which makes of a cytoarchitectonic field (in this case, the area gigantopyramidalis) a physiological entity. This field is a kind of mosaic of points each of which represents a single muscle, or a muscle group (or even perhaps a movement, for it is not quite clear what Fulton holds on this point). Apparently only simple movements are thought to result from the activity of this region. Indeed, it would seem that what is called "motor power" is—in some undefined and indefinable way—represented here rather than "movements." This field is sharply bounded in every direction, and as we cross its anterior border we enter abruptly another cytoarchitectonic-physiological field. In this are represented movements of quite another order, exemplified by the "highly integrated movements of the digits," and here representation is in a measure bilateral.

This field—or organ—is also sharply limited by surrounding and differentiated fields, whose functions presumably are equally sharply differentiated.

The essential feature of this conception of cortical motor representation is that this embodies two quite distinct mechanisms, each co-terminous with a distinct cytoarchitechtonic field, each with its own separate functions, and each sharply circumscribed by anatomical boundaries. This is a conception that might be attractively depicted in a diagram, and we may be sure that it is in a diagram only that it can have any existence.

At the other extreme we have the view that is exemplified in the writings of Lashley. Here, any topographical localization of function in the cortex is frankly regarded as a fiction. Even the representation of the retina in the calcarine cortex is questioned by this school, whose doctrines are in a measure a reversion to that early view of Taine (cited by Hughlings Jackson) for whom "the brain is a kind of polypus, whose elements have the same function."

Between these extremes stands the conception of cortical representation formulated by Jackson. Apparently, this is as far ahead of much current neurological thought as it was in Jackson's own time, and it obtains no attention from either of the two schools we have mentioned. Perhaps the views of Lashley are a natural reaction from the rather naive "jig-saw puzzle" hypotheses of cortical localization, but it seems probable that in Jackson's views is to be found the common ground on which both schools might meet and resolve their differences.

Jackson's doctrines nowhere find a single comprehensive expression, but are to be found scattered throughout his various papers. The following brief statement embodies—it is believed—their essence.

It is not necessary to recapitulate his conception of three levels of function; highest, middle and lowest, for his teachings on this point are widely known. It is particularly the highest and middle levels which concern us here, for the cerebral cortex provides their anatomical substratum. The excitable motor cortex of the physiologist is the seat of the "middle level" of motor function. It has been evolved out of the lowest level, and in it are re-represented, or re-coördinated, the simple and general movements represented in the lowest level. This re-representation consists in the synthesis of complex and special movements out of the simpler elements of the lowest level, and the experimental observations of Leyton and Sherrington have lent detail and confirmation to this conception.

For Jackson, the "præfrontal region" is the seat of his highest level. Here there takes place a further analysis and synthesis of movements represented in the middle level into the most complex and special movements of which the organism is capable.

There are no "abrupt" localizations in these two levels, and *all* movements are widely represented throughout them. Thus, Jackson says "the 'arm centre' in the Rolandic region is for me a centre representing movements of all parts of the body, but yet movements of the arm very much more than any other movements." Again, "the central nervous system knows nothing of muscles, it only knows movements. . . . There are, shall we say, thirty muscles of the hand, these are represented in the nervous centres in thousands of combinations—that is, as very many movements. It is just as many chords, musical expressions and tunes, can be made out of a few notes." He gives examples of this multiplicity of representation, and a familiar example will occur to the clinician. Thus, in a partial hemiplegia, voluntary extension of the wrist is often lost while the power of voluntary clenching of the fist is retained. But in the latter movement the wrist is strongly extended. This is to say, one representation of extension of the wrist is lost, but another and slightly different one (as a synergic movement) remains. Again, conjugate deviation of the eyes has no representation within the true motor cortex as a primary movement, but only as secondary to rotation of the head. Its representation as a primary movement lies elsewhere in the second frontal convolution.

These various representations necessarily require a great " quantity " of grey matter, and Jackson says " it is equally obvious that the larger quantity of grey matter representing numerous different movements must be made up of a great number of separate parts. Each movement, so far as it differs from all others, must have so far special representation in the nervous centres. Greater differentiation of function implies greater physical separation, however little different the movement may be from other movements, and however much of it may be a recoördination of other movements. So far as there is a degree of independence of movement, so far must there be a degree of separateness of representation of that movement by different cells in the nervous centres. And yet, of course, the separation is not isolation ; on the contrary, the greater the differentiation, the more complete the integration of the different elements, for they have to act together or in succession . . . I do not believe that nervous centres represent limited regions of muscles, nor even isolated groups of movements . . . any part, especially such a one as the hand, is represented in innumerable places."

This quality of representation accounts for the lack of symptoms after local destroying lesions, and when any loss of function does ensue from such a lesion recovery takes place not because other units have taken on functions they never had before, but because those units, having functions closely similar to those of the units destroyed, they can act nearly as well for the functions of both. This is Jackson's *principle of compensation.*

But on this basis compensation can never be absolute, a fact which is also familiar to the clinician. Thus, the victim of a cerebral thrombosis who appears on routine examination to have made a perfect recovery is nevertheless usually aware that some special movements of the affected hand and digits are gone for ever. If he previously played some musical instrument, he finds that his hand has lost some of its cunning for the task—some of his " special " movements have been lost.

It is perhaps not surprising that those whose studies of the effects of cerebral lesions are confined to the monkey, or to some lower animal, should suppose that recovery can be absolute. The animal, with its scanty repertoire of special movements has not so much to lose, and the really detailed examination of its motor functions is necessarily difficult, if not impossible.

We see, then, that on this view of cortical localization the absence of symptoms after a local destroying lesion does not mean that there is no local representation. On the contrary, it bears witness to the complexity and highly specialized character of that representation.

This theory of the cortical representation of movements postulates no "jig-saw" puzzle of rigidly defined, separate local elements on the one hand, nor an undifferentiated cortex acting by mass on the other. These opposing notions we might almost define as being "differentiation without integration," and "integration without differentiation" respectively. Jackson's conception allows of the special representation of every possible movement, and is compatible alike with the absence (or paucity) of symptoms after local destroying lesions, and with the spread and sequence of convulsion in states of instability of grey matter. It truly represents "differentiation with integration," and would appear to be the only possible valid generalization of all the varied facts of clinical and experimental observation.

And while Jackson placed his highest level of cortical motor function in the frontal lobe anterior to the excitable cortex, he did not separate it from the middle level by any such arbitrary cytological boundaries as are inherent in the view postulated by Campbell and adopted by Fulton.

The conclusion we have reached, then, is that neither on anatomical nor upon physiological grounds can we accept the division—of structure and of functions—made by Fulton of the cortical region lying anterior to the fissure of Rolando. It remains to summarize the actual facts of observation recorded by him and his collaborators.

As far as it is possible to recognize two distinct syndromes resulting on the one hand from ablations within the precentral area, and on the other from ablations of the region immediately anterior to this, it appears that:—

(1) Ablation of the precentral gyrus, or of that part of it lying next to the fissure of Rolando, is followed by a hemiparesis conforming in character to Jackson's description given earlier, and resembling the slighter degrees of hemiplegia in man. Some hypertonus has finally developed in the most paralysed parts of the limb and the tendon-jerks have shown a corresponding increase. After cessation of recovery there has been a residual loss of some special movements of the digits.

(2) Ablation of the region lying immediately anterior to the last considered is followed in the chimpanzee by a very fugitive hemiplegia, which is either a "neighbourhood symptom" or more probably due to actual encroachment of the lesion on the motor area, properly so-called. The sole residual defect appears to resemble that known to clinicians

as motor apraxia. Permanently enduring forced grasping does not ensue except in bilateral lesions of this region.

(3) Ablation of the frontal convolutions anterior to both the preceding regions is followed, not by paralysis or spasticity, but by a loss of spontaneous motor activity on the part of the animal, with a tendency to perseveration and slowness of movement. Phases of restlessness may also appear.

(4) Forced grasping may appear, both in man and in apes, apart from either paralysis or spasticity, and cannot therefore be regarded as an integral part of a syndrome in which all three are invariably present.

(5) The so-called "premotor syndrome" is predominantly a syndrome of the true motor cortex and follows lesions within this experimentally delimited region.

(6) There is only one kind of hemiplegia, though several degrees of this, and it is seen only in association with lesions involving the true motor cortex and/or the pyramidal tract.

(7) The more extensive the destroying lesion of the cortex in the region immediately anterior to the fissure of Rolando, the more severe the degree of hemiplegia resulting and the more marked the residual defect. Accompanying this severe degree of hemiplegia there is commonly more marked hypertonus.

In conclusion, there remain many problems in determining and analysing the disorders of motor function which ensue upon lesions of the anterior parts of the frontal lobes. Some of these disorders have been glimpsed in the course of the experiments we have considered and many others are familiar to clinicians. It is hoped to attempt some discussion of these in a subsequent paper.

ADDENDUM.

Since this paper was written another contribution to the subject has appeared (*Proc. Californian Acad. Med.*, 1933-34), in which Fulton gives for the first time a comprehensive definition of what he understands by the term "motor cortex." It is as follows: "The motor area is defined histologically as the region of the cortex containing in its fifth layer the large cells of Betz. It should be emphasized that the limits of the motor area are determined by its cellular structure and not by its electrical excitability."

The author does not indicate to his readers that the above usage of the term in question differs essentially from that hitherto generally adopted. It is perhaps better, therefore, not to regard it as a scientific definition but as something in the nature of a private ruling that a term which has always rightly been applied to a certain cortical region in virtue of certain properties revealed by it, shall henceforth be applied to something different; namely, to a cortical region which contains pyramidal cells exceeding certain arbitrarily determined and inconstant dimensions. Such a reading of the term "motor cortex" lacks both physiological value and anatomical precision, and cannot be made the basis of any hypothesis of cortical motor functions.

However, in concluding the discussion of this subject it may be noted that Fulton employs this special definition of the "motor cortex" only in connection with the investigations considered in this paper. Where he is not concerned with the functions and syndromes of the premotor cortex, he appears to employ the term "motor cortex" in the generally accepted sense. Thus in a paper with Dusser de Barenne (*Journ. Cell. and Compt. Physiol.*, 1933, **2**, 399), the terms "motor" and "excitable" as applied to the cortex are used as synonymous, and figures are given in which the motor cortex is depicted as of considerably greater extent than the area gigantopyramidalis. In these circumstances, it may not be an unjust inference that theoretical considerations have had undue weight in the formulation of the arbitrary definition to which objection has been raised here.

Further, the paper contains what appears to be an important modification in the description of the "premotor syndrome." As originally described, the essential defect symptom was a loss of highly integrated digital movements, but this symptom is now said to be in the nature of "an intellectual deficit" in consequence of which the subject has *forgotten how* to perform certain learned movements and has to relearn them. While this mode of expression involves a flight to psychological terminology, it does indicate what is probably a more correct assessment of the motor defect described by Jacobsen after ablation of the premotor area in the chimpanzee. Nevertheless, it profoundly modifies the original description of the premotor syndrome. Further, since Fulton regards the premotor cortex as the cortical representation of the "extrapyramidal motor system," we have the paradoxical conclusion that a destroying lesion of this system produces as its characteristic symptom "an intellectual deficit." This involves an entirely new conception of the functions of the extrapyramidal system.

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THE DISORDERS OF MOTOR FUNCTION FOLLOWING AN ABLATION OF PART OF THE "LEG AREA" OF THE CORTEX IN MAN.

BY F. M. R. WALSHE.

In the preceding paper (p. 49) the results of a partial, destroying lesion of the physiologically delimited motor cortex were summarized as follows: (i) The immediate result is a widespread paralysis of movements of the affected limb, the special and varied movements of the distal part of the limb being most severely paralysed; (ii) the large and simple movements of the proximal part of the limb recover early and completely, the special and more varied movements of the distal part recovering more slowly and less completely, so that some of them are permanently lost or impaired; (iii) hypertonus develops in the most severely paralysed parts of the limb; and (iv) the tendon-jerks become and remain increased.

This state of affairs corresponds to the description given by Jackson of partial hemiplegia and to the findings of Leyton and Sherrington in the chimpanzee and of Horsley in man.

It was noted, however, that Fulton employs the term "motor cortex" in a special sense, restricting it to the area giganto-pyramidalis. The syndrome summarized above he attributes to a lesion of the "premotor cortex" and of its hypothetical extrapyramidal projection system. He would therefore regard the cortical ablations of Leyton and Sherrington and of Horsley as predominantly "premotor."

From what we have learned of the distribution of the area giganto-pyramidalis it will be apparent that a pure ablation of this area is practicable only at its superior extremity, where its antero-posterior extent is considerable—some two centimetres in the adult human brain—and is not practicable elsewhere since the area in question is buried in the anterior wall of the fissure of Rolando lateral to the superior genu. Indeed, the motor representation of hand and finger movements in the cortex lies almost wholly frontal to the area gigantopyramidalis and contains relatively few "giant cells." That is to say, the representation of these movements is a function of Fulton's "premotor cortex" and its extrapyramidal projection system; a corollary to their hypothesis which Fulton and his collaborators do not appear to have appreciated.

If, then, in man we are to study the results of a pure "motor cortex" ablation (in Fulton's special sense) it can only be by the ablation of the superior extremity of the area gigantopyramidalis, of that part wherein movements of foot and toes are represented. In this region such an ablation is practicable.

Through the kindness of Dr. Gordon Holmes the writer has had an opportunity of examining, both before and after operation, a patient in whom an ablation of the superior extremity of the area gigantopyramidalis was performed. He has also enjoyed the advantage of access to Dr. Holmes' exhaustive notes of the case made over a long period of time.

The ablation was one to which it cannot be objected that it encroached upon Fulton's "premotor cortex." Moreover, the case had the unique merit that the motor and reflex condition of the lower limb was entirely normal prior to the ablation. Thus all the changes effected in the limb by the ablation may be attributed to it. In this the case had advantages over Horsley's and Bucy and Buchanan's cortical ablations in man, in both of which the limb was not wholly normal before operation.

We may precede the record of this case by stating that the results of the ablation corresponded exactly with the syndrome summarized in the opening paragraph of this paper, and in no way resembled Fulton's hypothetical syndrome of the "motor cortex" in man.

E. L., an intelligent and educated girl, aged 11, first came under observation in 1933 with the following history: In 1929, at the age of 7, she began to be subject to attacks of "spasm" in the left foot and leg. These recurred with varying frequency until 1933, when she came under observation. They occurred at night. She awoke to find the left foot and leg rigid and her "head in a whirl." If she got out of bed she found the left leg so weak that she fell. Sometimes, also, the left arm "went limp" so that she dropped anything held in the left hand.

Enquiry revealed that the attacks were of three grades of severity:—

Severe attacks.—She wakes up, the left leg is rigid, the foot rigidly plantar flexed and inverted. Consciousness is never impaired, but sometimes she feels that she cannot breathe. The right leg may also go rigidly straight, but the face and right arm are never affected. In a few seconds the left leg "jerks and trembles." Headache comes on during the attack and may persist for some hours. The attacks last for from thirty to seventy-five seconds. When it subsides the left leg remains weak for some minutes and feels "like a strange piece of warm flesh."

Milder attacks.—Onset as above, but the left leg only affected. The foot goes rigid, the knee may be rigidly extended or may draw up. The attack lasts for from twenty to sixty seconds. If standing she has to seek support since the left leg is very weak, and so remains for a short time.

Slightest attacks.—These consist solely in a feeling of numbness in the leg and foot lasting for some seconds and accompanied and followed by weakness of the leg. There is neither stiffness nor movement of the leg.

Examination at this time (1933) revealed no abnormal physical signs in the nervous system. The left leg was normal in every respect, but on one occasion a slight attack was observed and was found to be followed by the transient appearance of an extensor plantar response in the left foot.

Repeated examinations over a period of three weeks failed to reveal any abnormality in the left leg, or elsewhere.

In July, 1934, the attacks increased greatly in frequency, as many as fifty a day being observed. An attack invariably occurred at the moment of falling asleep. Repeated examination of the nervous system revealed no abnormal physical signs.

In November, 1934, the attacks were becoming more severe and occurred at all times. The leg was more rigid in the attacks. She fell if standing unless she grasped a support. The left arm tingled, went stiff and shook in the more severe attacks. The face remained unaffected, and consciousness was never impaired. At times the left foot "felt funny" and the toes were not under complete control. From three to eight attacks occurred daily.

Repeated examination in the intervals between attacks revealed no abnormal physical signs in the nervous system; the movements, tone, sensation and the reflexes in the left leg being normal.

In December, 1934, from four to six attacks occurred daily. They began with an indescribable feeling in the left toes and foot, which ascended the limb to the waist. This might pass off without any ensuing spasm, but sometimes the foot began to tingle, then to draw up. Sometimes the knee drew up also. The left arm became stiff and weak. Clonic jerks developed in both arm and leg. Some transient weakness of both arm and leg ensued. In what the patient called "all over attacks" the right limbs also jerked, but less violently than the left. The face was never involved, and speech and consciousness remained intact.

Examination on one occasion shortly after an attack revealed increased tendon-jerks in the left leg, and a tendency to ankle clonus. The abdominal and plantar reflexes were all normal. There was a defect of postural sensibility in the left toes, but other modes of sensation were normal.

On all other occasions the state of the limb was normal—and so remained until after operation.

On December 20, 1934, the right cerebral cortex in the Rolandic region was exposed (Mr. Julian Taylor). No abnormality of appearance, tension or consistency was found. The "arm area" was found by faradic stimulation to be unexpectedly high on the ascending frontal convolution, and the area from which movements of the foot and toes could be elicited lay mainly on the mesial aspect of the hemisphere. This region was then excised by a diathermic knife.

Subsequent *histological examination* (Dr. Greenfield) of the fragment of cortex removed (1·5 cm. in antero-posterior dimensions) revealed that its caudal portion had the structure of granular post-central cortex, but anterior to this and to the extreme frontal end of the fragment numerous Betz cells were found. Thus, the frontal limits of the area gigantopyramidalis were not transgressed.

Seven hours after operations.—The patient was fully conscious and comfortable. There was total loss of voluntary movements of foot and toes, left ankle clonus and a left extensor plantar response. There was impairment of postural sensibility in the hallux.

Thirteen days after operation (re-examination by G. H. and F. M. R. W.).—There is a trace of paresis of the left lower face on smiling, but not on movements carried out to order. There is slight paresis and slowness of finger movements, especially of isolated finger movements. The outstretched left arm droops slightly. Its tendon-jerks are brisker than those of the right arm. The tone is normal. The abdominal reflexes are present bilaterally, but are brisker on the right side.

The left lower limb is not wasted. Its vascular condition is normal. There is total loss of voluntary dorsiflexion, inversion and eversion of the foot. There is no dorsiflexion of any of the toes, but feeble plantarflexion of the two outer toes only. At the knee both flexion and extension are weak, the former more so than the latter. At the hip extension and adduction are slightly weak, flexion and abduction are weaker. All movements of the limb are slow and clumsy, and she can just fling up the extended leg so that the heel clears the bed by about 6 in. The right knee and ankle jerks are normal, the left greatly exaggerated and there is clonus at the left ankle. The right plantar response is flexor, the left extensor. There is no hypertonus of the hip muscles, but slight of the knee extensors. There is considerable spasticity of the dorsiflexor muscles of the ankle and foot.

There is slight impairment of postural sensibility in the toes, but cutaneous sensibility is normal.

Fifty days after operation.—Movements at the hip are now of normal strength, knee flexion remains slightly weak. There is weak dorsiflexion, inversion and eversion of the foot. All toe movements are defective. Left ankle clonus and increased knee and ankle jerks remain. The plantar response is extensor. Sensibility is unchanged since last observation.

Summary.—Circumscribed ablation of that portion of the area gigantopyramidalis from which movements of foot and toe could be elicited on faradic stimulation is followed by total loss of all movements of the foot and toes, and by impairment of all movements of the limb—least of those of the proximal segment of the limb. Rapid recovery of movements of the proximal part of the limb ensued, but movements of the foot and toes still remained grossly defective after fifty days. Hypertonus developed early in the most paralysed parts of the limb, and tended to increase in degree with the passage of time. Increase in the tendon-jerks was also an early phenomenon, clonus appearing within a few hours and persisting undiminished after fifty days. The plantar response was extensor in type from the outset. There was an initial "neighbourhood" paresis of the face and arm, which soon disappeared.

CONCLUSIONS.

In this case of localized convulsion of the left leg, beginning in the foot, the limb was in every respect normal in movements, tone and reflexes up to the moment of operation. The residual abnormalities that are described above may thus be attributed in their entirety to the cortical ablation.

Both macroscopically and microscopically the lesion was within the area gigantopyramidalis, and therefore is—even in Fulton's arbitrary connotation—a pure "motor cortex" ablation. The residual state of the limb was one in which restoration of the movements of the foot and toes remained incomplete, hypertonus and increased tendon-jerks appeared, with ankle clonus and an extensor plantar response.

This is the syndrome described by Leyton and Sherrington in the chimpanzee and by Horsley in man, and corresponds to the picture of partial hemiplegia given by Jackson in respect of the loss of movements. It does not resemble Fulton's "syndrome of the motor cortex" in man, which we may therefore conclude to have no real existence.

With the single exception of "forced grasping" we may also conclude that Fulton's syndrome of the "premotor cortex" in man is in reality a syndrome of the true motor cortex, and has nothing to do with a histologically and physiologically differentiated "premotor cortex" and its extrapyramidal projection system.

The writer wishes to express to Dr. Gordon Holmes his thanks for the opportunity of observing and recording this case.

DIABETES INSIPIDUS.

BY J. H. BIGGART.

(*Laboratory of the Scottish Asylums Board, and Department of Pathology, Edinburgh University.*)

SINCE Thomas Willis [38] in 1674 differentiated between diabetes mellitus and diabetes insipidus many theories have been evoked to explain the pathogenesis of the latter disease..

Following the recognition of a diabetes insipidus the issue was made rather involved by the description of oxaluric diabetes, hippuric diabetes, phosphaturic diabetes and albuminuric diabetes. However, in 1841, Lacombe [23] gave a good clinical description of diabetes insipidus, and with the subsequent work of Bernard [4], this was established as a definite clinical syndrome.

Since that time there have been three main epochs in the history of the syndrome. The first dates from 1860 when Bernard produced a similar syndrome in rabbits by puncture of the floor of the fourth ventricle. Such a puncture produces a polyuria of low specific gravity which, however, clears up in a few days. Bernard's results were verified by Eckhard [13], Jungman and Meyer [20], and amplified by those of Kahler [21], who succeeded in producing a permanent polyuria by the injection of silver nitrate solution into the medulla in the neighbourhood of the restiform body. More recently Dresel and Lewy [11] came to the conclusion that the area concerned was in the floor of the fourth ventricle, medial to the spinal tract of the trigeminal nerve, ventromedial to the restiform body and dorsal to the nucleus of the seventh nerve. When such were the results of physiological experiment it is not surprising that the attention of pathologists was focused on the floor of the fourth ventricle to the exclusion of the rest of the brain. Thus Mosler [27] describes a case associated with a tumour of the fourth ventricle. There is no description of the hypophysis. Fink [15] gives a review of the autopsy reports during this period which shows the absence of microscopic studies, and the varied nature and sites of the lesions deemed responsible.

Following the work of Schäfer and Magnus [26 and 34], and Herring [18] on the active principle of the posterior hypophysis and its relation to diuresis the second period in the history of the disease may be said to have begun. At first it was believed that the posterior lobe extract produced a diuresis, and hence that diabetes insipidus could be explained on the assumption that this gland was overacting. The importance of the hypophysis as an ætiological factor was further demonstrated by the experiments of Cushing [8] (1910-1914), who succeeded in producing the syndrome by hypophysectomy. Whilst the importance of this gland in the production of the syndrome became accepted, there remained some doubt as to whether hypo- or hyper-function was the basis of its action. Finally, in 1913, Farini [14] and Van Der Velden [47] showed the controlling influence of injections of posterior lobe extract on the polyuria, and it became accepted in Germany, England and America that the syndrome was the result of hypofunction of the posterior hypophysis.

Meantime in France, Camus and Roussy [5] (1913), following up the work of Aschner [1], initiated the third and present theory of the pathogenesis of the syndrome. They showed that hypophysectomy in itself did not produce a polyuria, but that in those animals which developed the syndrome microscopic examination always revealed a lesion in the floor of the third ventricle. This view was confirmed by Leschke [24], Houssay [19], and Bailey and Bremer [2], who succeeded in producing polyuria by injuring the infundibulo-tuberal region. Richter [32], more recently, has succeeded in producing a permanent polyuria in rats by puncture of the hypothalamus anterior to the tuber cinereum, in the region of the chiasma. The occurrence of diabetes insipidus in encephalitis lethargica, whether in the acute phase or as a sequela, has further emphasized the importance of the hypothalamus in the pathogenesis of the disease.

The pathologist is thus confronted with the remarkable facts that diabetes insipidus is a syndrome produced by a lesion of the anterior hypothalamus, but controllable by injections of posterior hypophyseal extract.

The following three cases were studied in an attempt to correlate these observations:—

Case 1.—The patient was a nurse, aged 30. She gave a history of amenorrhœa for two and a half years. Vision had been blurred for six weeks and for six days before admission there had been a central scotoma of the left eye.

Clinical examination showed moderate progressive acromegaly with bitemporal hemianopsia.

Mr. Dott operated and removed a large pituitary adenoma by the right transfrontal approach. The patient recovered well after the operation but was found to have a post-operative diabetes insipidus. Full vision returned and apart from the polyuria she became perfectly well, and was able to return home. It was possible to control the polyuria by injections of pituitrin—1 c.c. four times per day. Six weeks after her return home patient developed some obscure cerebral catastrophe and was re-admitted unconscious. She died within a few hours.

At post-mortem the adenoma was found to have been almost removed, a small fragment being adherent in the recess at the right of the optic chiasma and about the anterior end of the right optic tract. The cause of death was not clearly ascertained.

Histological examination of the adenoma showed that it was composed very largely of eosinophil cells, the alpha granules staining quite well. The adenoma was large and had destroyed the posterior lobe. No pars tuberalis could be found. The hypothalamus showed a small nodule of unremoved adenoma. Small areas of softening were present in this region. Around each area of softening there was a dense astrocytic region, the astrocytes showing sign of division (two nuclei) and having swollen cytoplasm—"gemästete cells." Inside this zone of gliosis were numerous compound granular corpuscles. The areas involved are shown in figs. 1 and 2.

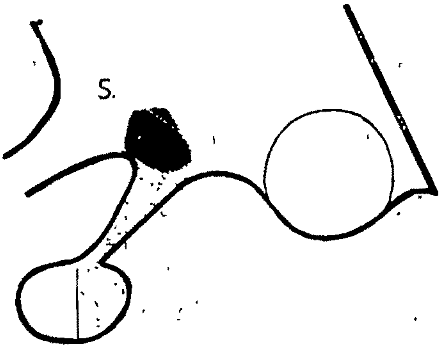

FIG. 1.—Case 1. Diagrammatic representation of area involved by the injury. It will be noted that the fibres coming from the nucleus supra-opticus to the posterior lobe of the hypophysis and the pars tuberalis are interrupted. S = Nucleus supra-opticus.

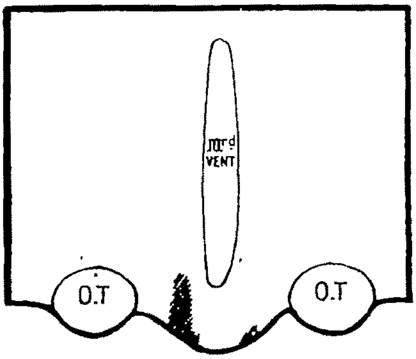

FIG. 2.—Case 1. Diagram illustrating the extent of the lesion on coronal section. The tuberal region has escaped. O.T. = Optic tracts.

It would seem that these areas represent the result of injury at operation, and as the diabetes insipidus was of post-operative onset it is permissible to regard these as the essential lesions in this case.

Case 2.—The patient was a man, aged 57 years. In 1931 he complained of retro-sternal pain in the left side of the chest. The heart action was satisfactory, though there was occasional irregularity due to extrasystoles. The

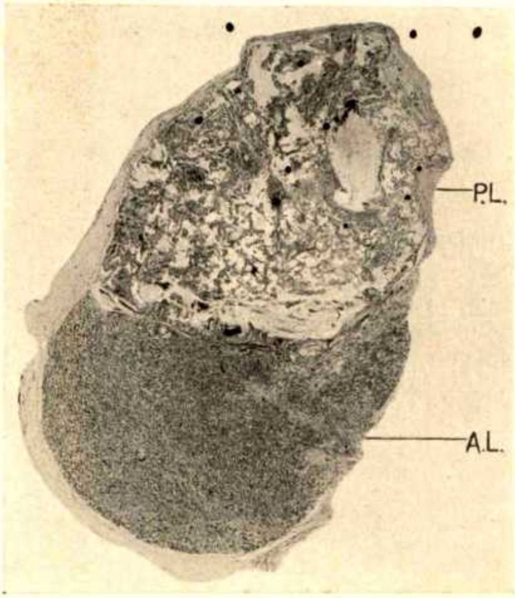

FIG. 3.—Case 2. Section shows the anterior (A.L.) and posterior (P.L.) lobes of the hypophysis. Stained H. and E. Magn. 8 diameters. The posterior lobe is completely occupied by a mucin-secreting papillary adeno-carcinoma. The pars tuberalis is also destroyed.

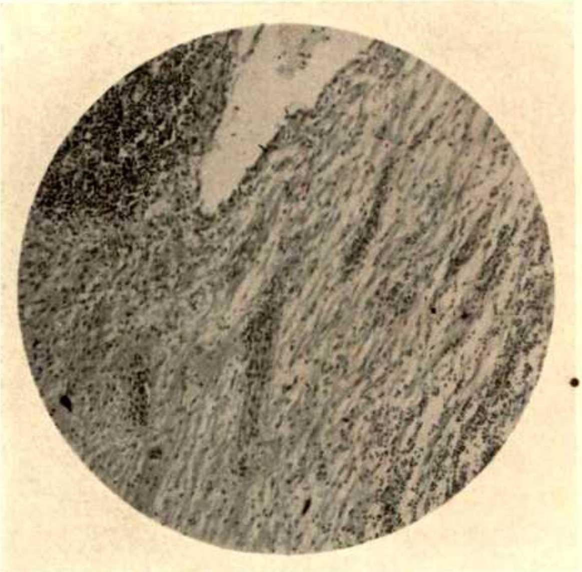

FIG. 6.—Case 3. Section through upper part of the infundibulum. There is gross infiltration with mononuclear cells. H. and E. Magn. 100 diameters.

To illustrate paper by J. H. Biggart.

blood-pressure some years ago ranged between 150 and 160 mm. Hg., but recently it had been about 115 mm.

In June, 1933, patient began to experience intense and almost continuous thirst, and to pass very large quantities of urine. The urine was of low specific gravity and contained no albumin or sugar. The condition was diagnosed as diabetes insipidus. It was controlled by injections of pituitrin—1 c.c. twice daily.

Two months after the onset of the polyuria the patient began to suffer from headache. This was generalized in character. His doctor noticed some papillœdema of the left eye. This slowly progressed in both eyes. There was also a complaint of tinnitus. The blood Wassermann was strongly positive.

Examination showed a somewhat emaciated man. The cranial nerves were normal with the exception of some papillœdema and a few hæmorrhages in the left retina. Except for a slight degree of arteriosclerosis the general examination was negative. The Wassermann was positive in the cerebrospinal fluid, and the protein showed a definite increase. X-ray showed no deformity of the sella turcica, or clinoid processes.

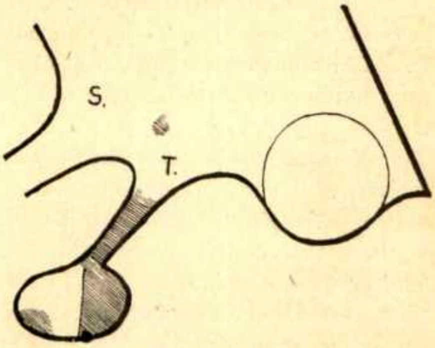

FIG. 4.—Case 2. Diagram to show the site and extent of the metastases. Note that the tuberal region is relatively uninvolved. Fibres from the nucleus supra-opticus to the posterior lobe of the hypophysis are destroyed. S = Nucleus supra-opticus. T = Tuber cinereum.

The clinical opinion was that the patient was suffering from an inflammatory process involving the basal meninges and the tuber cinereum—probably a basal syphilitic meningo-encephalitis with consequent polyuria, fluid obstruction and some degree of hydrocephalus.

A bilateral subtemporal decompression was performed by Mr. N. M. Dott on October 22, 1933.

For two days patient was very well, but on the afternoon of the second day he developed a rigor. After two hours the temperature rose to 102° F., the heart became irregular, and the pulse feeble. Thirty-six hours later he died.

At post-mortem only the brain could be examined. The meninges were thin and translucent. On section of the brain many small jelly-like nodules were found scattered throughout its substance. One such nodule had entirely replaced the posterior lobe of the hypophysis and the infundibulum. Microscopic studies showed that the small nodules were tumour tissue, the tumour being a mucin-secreting papillary adeno-carcinoma. The whole of the posterior lobe and stalk was found replaced by the growth, and no pars tuberalis could be identified around the upper end of the infundibulum. A small nodule was also present in the tuberal region above the ventral nucleus (Plate I, fig. 3). There was no evidence of a syphilitic basal meningitis. The anterior lobe of the hypophysis showed a small metastasis at its antero-inferior pole. The general distribution of the tumour in the diencephalic region was found by serial section, and is shown in fig. 4. Whilst deposits were numerous in the cerebral cortex, and not infrequent in the cerebellar cortex, there were none in the brain-stem or medulla.

The nature of the tumour suggests that it is a secondary deposit from a tumour of the alimentary tract.

Anatomical diagnosis: Multiple carcinomatous metastases in brain; (?) primary growth in alimentary tract; replacement of posterior hypophysis and infundibulum by tumour; metastasis in hypothalamus.

Case 3.—The patient was a female, aged 54 years. She complained of thirst and polyuria, which had begun seven weeks prior to admission to the Royal Infirmary. The onset of these symptoms was accompanied by headache of a generalized nature. A few days after the onset of the illness the patient had attacks of vomiting which were unrelated to the taking of food. She gradually lost weight.

On examination she was found to be rather drowsy and stupid. The skin was dry, harsh and inelastic. There was an internal strabismus of the left eye. On admission she had Argyll Robertson pupils, but on examination a few days later the pupils were found to react normally. The other cranial nerves were normal, and general examination revealed no abnormality except an inflamed throat. Temperature normal; pulse 90; respirations 20. The urine contained no sugar, albumin or acetone. Its specific gravity was 1,003.

Whilst in hospital the patient was noticed to drink large quantities of fluid and to suffer from polyuria. This was not controlled by injections of pituitrin. A week after admission she developed a temperature and her pulse-rate increased. Her throat became markedly inflamed and she developed a painful inflammation below the angle of the jaw on the left side. She continued in this state for some days and then developed a bronchopneumonia, and died three weeks after admission.

At post-mortem the main findings were marked inflammation of the tonsils and pharynx with involvement of the tissues of the neck, acute splenic tumour, and toxic changes in the liver, kidney and heart. There was congenital absence of the left kidney. The brain showed marked congestion of its surface with small subarachnoid hæmorrhages. The pituitary and infundibulum appeared normal.

On section of the fixed brain there was no gross change except congestion. Histological examination showed an encephalitis affecting the medulla, the periaqueductal region of the mid-brain, the substantia nigra and the anterior hypothalamus. There was no demyelinization. In the regions affected there was marked perivascular cuffing with lymphocytes and plasma cells, and some destruction of the ganglion cells. The process was most intense in the anterior part of the hypothalamus. In this region the area involved is shown in fig. 5. Apart from a little infiltration of the meninges over the corpora mamillaria the posterior hypothalamus was not involved. In the anterior region the nucleus supraopticus was completely destroyed, and was replaced by an area of intense gliosis, many of the astrocytes having large swollen, rather hyaline cell bodies. The nuclei of the tuber were also destroyed, and in serial sections scarcely a nerve-cell could be found. The inflammatory process extended into the upper part of the infundibulum which was grossly infiltrated with lymphocytes and plasma cells (Plate I, fig. 6). Some large globoid cells resembling "gemästete" glial cells were found in the stalk. The pars tuberalis was also infiltrated by inflammatory cells, though no degenerative changes could be appreciated in the glandular epithelium. The anterior hypophysis was normal, and the posterior lobe showed no changes. There was no increase in colloid or pigment. The infundibular process of the third ventricle was surrounded by a dense wall of gliosis, in which division of the astrocytes was still taking place.

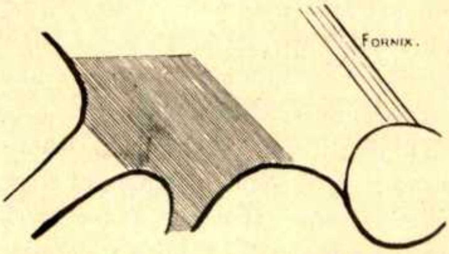

FIG. 5.—Case 3. Diagram to show the area of the hypothalamus involved in the encephalitis. The area includes the nucleus supra-opticus and the nuclei of the tuber cinereum and the upper part of the infundibulum.

Anatomical diagnosis: Acute tonsillitis; cellulitis of the neck; acute splenic tumour; toxic changes in all organs; history of diabetes insipidus; acute epidemic encephalitis; involvement of anterior hypothalamus, infundibulum and pars tuberalis.

DISCUSSION.

It will be seen that these three cases, whilst furnishing the same clinical syndrome, have a very varied pathogenesis, one traumatic, one neoplastic, and the third encephalitic. Apart from the cases Lhermitte [25] and others of the French school have traced to a syphilitic basal meningitis involving the hypothalamic region they cover the usual causes of the syndrome of diabetes insipidus. Fink [15], in his analysis of 107 cases, found that 63 per cent. had tumours of the base of the brain, 13 per cent. had syphilitic processes, 8 per cent. were due to non-specific inflammatory lesions, 5 cases showed tuberculosis, whilst 12 cases were due to trauma. It is probable that these figures give a somewhat erroneous impression, as it would seem from a review of the recent literature that diabetes insipidus is not uncommonly found in epidemic encephalitis.

All these cases have in common a lesion of the hypothalamus, whilst two of them (Cases 1 and 2) have a concomitant lesion of the hypophysis. Before discussing in more detail what nuclei and tracts are involved it is necessary to review the anatomy of this region. Greving [17], Pines [29], and Croll [10] following the earlier work of Cajal [6] and Tello [35], have demonstrated a bundle of unmyelinated fibres which, taking origin in the nucleus supraopticus, is distributed in the posterior lobe of the hypophysis, the supraoptic-hypophyseal tract. According to Cajal some of these fibres end in the pars intermedia, whilst a recurrent branch supplies the pars tuberalis. Other fibres end on the cells of the pars nervosa. It is generally thought that these are efferent fibres. Greving has also shown that the nuclei of the tuber cinereum send their fibres into the mid-brain—tractus tuberalis descendens. The experiments of Beattie, Brow and Long [3] suggest that hypothalamic fibres even enter the spinal cord.

The origin of the secretion of the posterior lobe is still unknown, but wherever it is formed it is probably not in the cells of the pars nervosa, which appears to consist of a rather specialized form of glia, a connective tissue frame-work and blood-vessels. Whether or not the colloid bodies described by Herring [18] and emphasized by Collin [7] and Cushing [9], are the histological evidence of the secretion there is no positive knowledge. The facts are that a biologically active substance can be extracted from the posterior lobe and the tuber cinereum, but that both of these areas are sheathed in an epithelial covering of glandular tissue—the pars intermedia and pars tuberalis—and it is most likely that it is in these glandular areas that the so-called posterior lobe secretion is manufactured. Ablation of the pars nervosa leads eventually to an increase in the "pituitrin" content of the tuber cinereum, but as this is accompanied by a hyperplasia of the pars tuberalis it is still conceivable that the secretion finds its way into the nervous tissue from the epithelial investment (Rubio [33], Trendelenburg [36]). The presence of the secretion in the nervous tissue seems at any rate to indicate the direction of its flow.

In 1930 Popa and Fielding [30] described a peculiar venous return from the hypophysis. The sinusoids of the glandular portions collect into veins which ascend the stalk, and there break up into capillaries around the nerve-cells of the tuber cinereum. They named this the hypophyseal-portal system. If one is permitted to reason from this anatomical finding it would appear that it represents a mechanism for bringing the secretions of the hypophysis into relationship with the nerve-cells in this region. Whether the path of absorption of the anti-diuretic factor be by this venous circulation, or along the interstitial glial network, appears to be a matter of little note. In either case it will arrive in contact with the nerve-cells of the tuber cinereum and perhaps also with those of the supraoptic and para-ventricular nuclei.

Assessed in the light of these anatomical findings it will be seen that in Case 1 (figs. 1 and 2) the supra-optic-hypophyseal tract is interrupted by the traumatic lesion. The cells of the nucleus tuberis and nucleus supraopticus are largely intact, though some of the cells of the latter nucleus show regressive changes. In Case 2 there is again interruption of this tract without any direct damage to the nuclei. The pars tuberalis is involved in both cases. In Case 3 there is destruction of both groups of nuclei with inflammatory involvement of the pars tuberalis. Clinically Cases 1 and 2 agree in both reacting to injections of the anti-diuretic factor of the posterior hypophysis. Case 3, however, failed to react. The injury of the various structures concerned is shown in Table I.

TABLE I.

	Case 1	Case 2	Case 3
Injury to Supra-optic-hypophyseal tract ..	+	+	+
,, ,, Nucleus tuberis	—	—	+
,, ,, Nucleus supra-opticus	Sl.	Sl.	+
,, ,, Pars tuberalis	+	+	Sl.
,, ,, Pars nervosa	+	+	—
,, ,, Pars intermedia	+	—	—
,, ,, Pars anterior	+	Sl.	—
Reaction to Pituitrin	+	+	—

The only anatomical difference of seeming importance is the integrity of the nuclei in Cases 1 and 2, and their absence in Case 3. This difference, however, seems to be of importance in that it points to a central action for the anti-diuretic factor, i.e., this secretion produces its action through one or other of the nuclei which have been destroyed in Case 3. That it is the tuberal nuclei through which this action takes place is rendered probable by the existence of the tractus tuberalis descendens, and by a consideration of the experimental work of the French school. Such a central action is further rendered probable by Cushing's experiments [9]. It is also supported by the fact that pituitrin will not control the polyuria whilst the patient is asleep (Labbé and Azerad [22]) or under anæsthesia. Cases refractive to pituitrin are also obtained experimentally by tuberal damage (Dreyfus [12]).

Whilst the French school (Gilbert, Villaret and Saint-Girons [16], Rathery [31]) divide diabetes inspidus into two types: (1) of hypophyseal origin, and (2) of nervous origin: it would seem, if this central action of pituitrin is admitted, that the two types can be reconciled.

The following figure is an attempt to explain these varied findings (fig. 7).

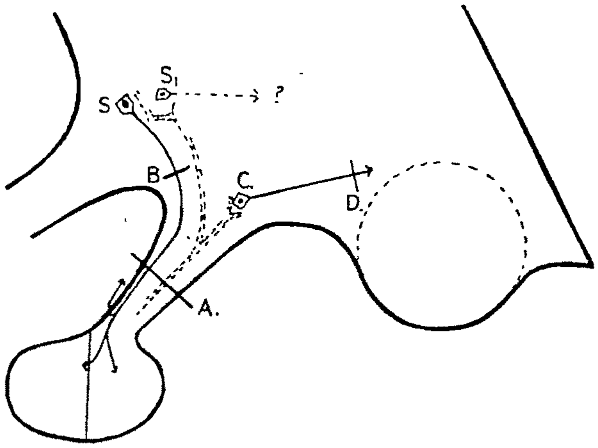

Fig. 7.—Diagram to illustrate the sites of the lesions producing diabetes insipidus (*vide* text). S = Nucleus supra-opticus; S_1 = the tract described by Greving; C = Tuberal nuclei; CD = Tractus tuberalis descendens; A, B, C, D represent possible sites of injury.

A lesion at "A" may produce a polyuria by interruption of the supra-optic-hypophyseal tract. This division would presumably lead to a diminution of the secretion of the anti-diuretic factor, but this would be compensated for by the pars tuberalis which escapes. In fact according to Rubio [33] the pars tuberalis will hypertrophy. A lesion at "B" will cut off the secretory fibres to the whole epithelial investment of the pars nervosa and pars tuberalis, and so lead to the establishment of a permanent diabetes insipidus. Such a case, however, will be controllable by injections of pituitrin as the effector pathway from the nuclei of the tuber cinereum is still intact (Cases 1 and 2). A lesion at C or D, however, which destroys the effector pathway (Case 3), will result in a polyuria which is refractory to treatment. According to Dreyfus such cases are rare in human pathology, and constitute but 5 per cent. of all cases of diabetes insipidus.

Such a theory would also embrace the experimental polyuria of Bernard and Kahler, and in the case of the permanent polyuria produced by the latter it would be proof of the theory if pituitrin were without effect.

It will be seen that the present explanation of the pathogenesis differs from that of many modern authors in that the lesions are considered paralytic in nature and not irritative. It is difficult to imagine a lesion which will continue merely to irritate over a period of years.

Whether or not complete destruction of the hypophyseal tuberal mechanism would eventually be compensated for by some lower centre remains a matter of conjecture. Newton and Smirk's [28] recent work on decerebrate hypophysectomized cats suggests that such a theory is feasible, and may explain the gradual disappearance of the polyuria in some chronic cases.

SUMMARY.

(1) Three cases of diabetes insipidus are described.

(2) On the basis of these and of the cases recorded in the literature an attempt is made to explain the mechanism by which the disease is produced.

I am indebted to Dr. Dott for the clinical records of Cases 1 and 2, and to Colonel Harvey of the Royal College of Physicians' Laboratory for the specimens. To Dr. Comrie I am indebted for the clinical record of Case 3.

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FAMILIAL DEGENERATION OF THE CEREBELLUM IN ASSOCIATION WITH EPILEPSY.

A REPORT OF TWO CASES, ONE WITH PATHOLOGICAL FINDINGS.

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THE primary cerebellar atrophies have always provided the neuropathologist with material for speculation and a considerable amount of attention has been devoted to the difficult task of separating them into various morphological types; difficult because there are relatively few cases in which the disease is limited to the cerebellum. In fact, it is well known that both the non-familial and the familial instances of this disease have presented manifold combinations of lesions of the cerebellar cortex and its connections in the brain-stem and spinal cord, with the result that numerous gradations exist between Friedreich's spinal ataxia and the cerebellar cortical atrophy of André-Thomas. They represent a heterogeneous group of cerebello-spinal degenerations which Raymond [1] would regard as examples of a premature physiological senescence localized to certain organic systems, and in which the histopathological picture is subject to individual or familial variations.

Certain fairly well defined types, however, can be recognized, and with regard to the so-called acquired cerebellar atrophies, most neurologists are willing to accept the triple division proposed by Marie, Foix and Alajouanine [2], viz.: primary parenchymatous atrophy of the cerebellar cortex (delayed cortical cerebellar atrophy); olivo-ponto-cerebellar atrophy, and olivo-rubro-cerebellar atrophy. From an anatomical standpoint such cases are exceptionally pure, though it is impossible to differentiate them clinically, and several transitional types have been described. Ramsay Hunt [3] has reported a case of primary atrophy of the dentate system in association with Friedreich's disease, and more recently Greenfield [4] described two cases of spino-cerebellar degeneration occurring sporadically in elderly patients.

Unfortunately adequate histopathological studies have been scanty and the number of verified cases of the cortical and olivo-ponto-cerebellar atrophies are scarcely more than twelve of each type, while the olivo-rubro-cerebellar atrophy is at present limited to one case. Moreover, the olivo-pontine type has shown occasional familial incidence, but the cortical type has not, unless one includes the four cases in one family described by Holmes [5], of which the only one verified showed an olivo-cerebellar atrophy.

It is with these facts in mind that the following report is made upon two epileptic brothers, each of whom developed a cerebellar syndrome in middle life. One of them has recently died from phthisis, thus affording an opportunity of examining his central nervous system, which revealed a pure cortical cerebellar atrophy As far as I have been able to study the literature, this appears to be the first case of familial degeneration in which the atrophy was limited to the cortex. The association with epilepsy is also unusual and deserves special consideration.

The family.—This consists of 12 children, 7 males and 5 females. Six of them are at present alive, and with one exception have all been recently examined by the author.

The father died at the age of 75, and is reported to have been strong and healthy. He was a chronic alcoholic, as was his brother and father, but he worked as an engine driver until 70. The mother, an only child, died at the age of 72, and was not related to the husband (no consanguinity). Her gait was apparently normal. There is, however, a strong history of tuberculosis, and her mother and two uncles died from this disease.

Of the children, No. 1, the eldest, is now 54, and shows no cerebellar symptoms.

No. 2 was killed in a pit accident at the age of 27.

No. 3 is 49 years of age, has not been examined, but is reported to be normal.

No. 4 (Case 1 described later) suffered from epilepsy since infancy; developed a cerebellar syndrome at 41; died of phthisis at 46.

Nos. 5 and 6 were twins and both died when 7 to 8 months old from marasmus.

No. 7 died when one month old from whooping-cough.

No. 8 (Case 2 described later) suffered from epilepsy since 19; developed cerebellar ataxia at 37; living, aged 41, an inmate of the South Yorkshire Mental Hospital.

No. 9, aged 40, shows no abnormality.

No. 10 was killed in the War at the age of 20.

No. 11 is now 37 years of age and must be regarded as a suspicious case. He is not epileptic but exhibits a fine tremor of the facial muscles when talking and his gait shows a slight defect of equilibration. When walking heel to toe he staggers a little and he also admits stumbling in the house, especially when tired. No other abnormality can be found and at present it is impossible to say with certainty that there is a cerebellar defect.

No. 12, aged 32, appears normal.

No further information could be obtained regarding the collateral lines, as apparently they are few and mostly extinct, and there is no history of any relative having suffered from ataxia or epilepsy.

The important features of the family history are the presence of excessive alcoholism on the paternal, and tuberculosis on the maternal, side. No member of the family has suffered from epilepsy with the exception of the two brothers described below.

Case 1.—Fred P., the fourth child of the family, had slight epileptic fits at the age of 3 years, but at 11 he was having definite major epilepsy occurring regularly both by day and night. At the age of 25 he began to show mental symptoms necessitating certification, and was, on June 3, 1913, admitted into the South Yorkshire Mental Hospital. His certificates state that he was violent and excited, threatening his mother and shouting that he was the "prophet of God" and the "Holy Trinity."

He remained in the hospital until his death at the age of 46. His first twelve years of residence were uneventful, and the records state that he was in good physical condition but a typical unstable epileptic, averaging three to six fits per month. At 38 he had an attack of typhoid fever from which he made a good recovery.

He was first noticed to be unsteady on his feet at the age of 41, when he frequently stumbled or fell down in the ward. A physical examination at about this period revealed a definite ataxia of both legs. He was then having three to four typical major fits every month, and his treatment consisted of luminal gr. 3 per diem. He was well nourished, of good physique and no skeletal deformities were noticed. The cardiovascular and respiratory systems presented no abnormality. A neurological examination, however, revealed well-marked inco-ordination of lower limbs. His gait was said to be like that of a drunken man, swaying unsteadily on a wide base. There was no Rombergism. The knee-jerks were present and equal and the plantar reflexes flexor. Normal abdominal reflexes were elicited. The pupils reacted normally to light and there was no nystagmus. Both arms showed definite inco-ordination during the finger-nose test, and his speech was slow, drawling and deliberate.

During the next two years his ataxia gradually increased, and at 43 it was found necessary to keep him more or less in bed. He died from pulmonary tuberculosis in May, 1933, at the age of 46.

Case 2.—Bertram P., the eighth child of the family, has been subjected to a more detailed clinical examination.

He was apparently healthy until the age of 19 when, as a result of his first epileptic fit, he fell off his horse during a gun practice of the Royal Field Artillery. More fits followed and he was discharged from the Army.

During the next thirteen years epilepsy became firmly established and he apparently indulged fairly frequently in alcoholic excesses. He carried on an occupation of groundsman, however, until the age of 33, when signs of mental instability appeared. He was then admitted into the South Yorkshire Mental Hospital in May, 1925, with a history of violence and excitement, attacking other people and threatening to injure himself. Physical examination revealed no abnormality and his gait was noted to be steady. He remained in the hospital for a period of five months, during which time he had three to four fits per month of both major and minor type. He was discharged and remained at home for the next six years under a more temperate régime.

At the age of 40, however, he became mentally unstable again and was re-admitted, but this time with a marked ataxic gait. Both the patient and his relatives report that he first began to be unsteady on his feet at about the age of 37. He is now 41 years of age, and the following account describes his condition at the present time.

He is of good physique and shows no muscular wasting. His height is 5 ft. 8 in. and his weight 10 st. 7 lb. In his general appearance there are no marked departures from normal and no signs of skeletal deformities, such as scoliosis or pes cavus. There is, however, a slight deformity of the left knee due to an old injury.

No abnormality can be detected in the cardio-vascular or respiratory systems. The blood-pressure is 110 systolic and 85 diastolic. The pulse is normal in rate and volume and there are no signs of arteriosclerosis. The urine shows no albumen or sugar and a blood-count revealed no noteworthy change.

The cerebrospinal fluid is clear, colourless, and not under pressure. The cells number 1 per c.mm.; total protein 0·06 per cent.; globulin slightly increased (Nonne-Apelt one plus); Wassermann negative; colloidal gold 0011221110. The spinal fluid thus shows a slight isolated increase of protein such as may be found in any degenerative condition of the central nervous system.

Neurological examination reveals a well-marked cerebellar symptom-complex as shown by a general disturbance of muscular co-ordination. As he sits in the chair a fine rhythmic tremor of the head is noticed, and there is a similar fine tremor of the hands and fingers as he rests one hand in the other. These static tremors are not constantly present but appear intermittently.

When requested to walk he stands up holding himself rigidly, fixes his eyes on the course to be taken, and with much deliberation and concentration starts off rather cautiously. He walks on a moderately wide base, swaying slightly from side to side and holding the head and trunk stiff and in a position slightly in advance of his lower limbs. His legs move in a stilted manner and his arms, though held stiffly, swing slightly at the shoulders. The hands look awkward owing to an unnatural extension of the fingers. In this manner he manages to walk fairly well, even with his eyes closed, and there is no tendency to deviate to either side of a straight line. But when he has to change direction or turn round, he immediately staggers and almost falls over. It is impossible for him to take more than two or three steps forward heel to toe, but there is no evidence of retro- or anteropulsion. Romberg's test is slightly positive, for though he can stand fairly still with his eyes open, he sways a little when they are closed.

Special cerebellar tests reveal a marked asynergy of voluntary movements in all four limbs. Such movements are carried out in an awkward and stiff manner, accompanied by a hypertonia of the muscles, an exaggeration of the associative movements, and an excessive display of force. The heel to knee is carried out with fair accuracy, though at first he is inclined to lift the heel high in the air before placing it either a little above or below the knee, but improvement is quickly gained on the second or third attempt. The finger to nose test is also performed with good orientation, both with eyes open and closed. When carried out quickly, however, there is a distinct hypometria, the finger always making an abrupt stop about 2 in. from the nose before being carried to its final destination. This sudden check is not followed by a recoil, and therefore constitutes a true "freinage" reaction (bradyteleokinesis) which the French attribute to a lesion of the cerebellum.

In this patient "freinage" can be elicited in both arms with the eyes open or closed, and when the finger finally rests on the nose there develops a slight unsteadiness or rubbing-in motion (defective fixation). When the test is carried out slowly, a slight intention tremor develops as the finger approaches its objective, but it is carried without a check to its termination only to be followed by the rubbing-in motion. The above phenomena can be equally demonstrated by the finger to finger test.

When asked to hold both arms out horizontally, they sway up and down, but do not deviate outwards. There is a marked dysdiadochokinesis during the pronation-supination test, the movements being slow, irregular and obviously requiring much effort. Manipulative movements of the hands are all performed in an awkward, clumsy manner, his fingers giving the impression of being "all thumbs." He is awkward when using scissors or buttoning up his clothes. When asked to toss a coin in the air he takes a long time to adapt the coin on his fingers, and when, with many facial contortions, he eventually jerks it in the air he is unable to catch it. The finger-thumb test as described by Holmes is carried out with fair success.

Writing is a very laborious procedure. He grips the pen tightly in his right hand and writes slowly without tremor, but with many pauses and occasional spurts, with the result that the letters are irregular, wavy and ragged. His attempt to draw a circle or a square demonstrates his inability to keep his pen on a straight course. The tendency to hypometria is also shown by his attempts to draw a straight line between two dots, for he invariably stops short of the second dot.

Experiments with Bárány's pointing tests give rather indefinite results. There appears to be a tendency to mispoint outwards from below upwards and downwards from without inwards, but both are inconstant and accuracy is quickly obtained. When asked to touch a point 10 in. above the bed with his foot, there is marked overflexion of the limb, and the left leg shows distinct unsteadiness and frequently falls short of the mark. With his eyes closed his attempt at writing a figure 8 in the air with his foot is quite good.

There is no evident hypotonia except perhaps in the arms. It is difficult to get him to relax, but there is a slight flabbiness at the wrist and the Stewart-Holmes rebound phenomenon is occasionally obtained. The muscles become hypertonic on every attempt at movement. Cerebellar catalepsy could not be demonstrated, and there is no apparent decomposition of movements. It is difficult for him to sit up from a dorsal position, and in doing so he raises both legs high above the bed. There is no paralysis or paresis of any muscle groups.

Speech is slow, monotonous, deliberate and characterized by frequent long pauses. He gives the impression that considerable effort is required to formulate his words, although he is able to shout.

All cranial nerves are normal. The pupils are equal, regular, and react well to light and accommodation. Ocular movements are normal in range and there is no nystagmus. A rough test of the visual fields shows no abnormality, and the fundi are normal. No vestibular defect could be found when using the caloric test.

The abdominal reflexes are diminished, but a definite contraction can be obtained in the umbilical region on both sides. A heavy blow is required in order to elicit the knee-jerks, but they are present, equal, and not pendular. The ankle and arm jerks are obtained with difficulty, and the plantar reflexes are both flexor.

No disturbance can be found in the sensory system—touch, pain, thermal, joint and stereognostic tests all giving normal results.

We may say, therefore, that this patient exhibits a profound general disturbance of all purposive movements, as shown by muscular inco-ordination and asynergy. Furthermore, there is a hypotonia during repose (arms) and a marked hypotonia during muscular action.

It is evident also that the cerebellar defect is to a great extent compensated by cerebral control and correction, for his every movement appears to require constant voluntary attention and effort. In fact, when cerebral influences are diminished or abolished, as frequently occurs during the temporary confusion following an epileptic fit, he is then unable to stand. and has been seen to spin round like a top.

Epileptic fits have been occurring regularly since admission with a frequency of four to six per month. They are typical epileptiform seizures of the grand-mal type and show tonic and clonic stages. No evidence of an aura can be elicited, and there is no opisthotonos suggesting the so-called cerebellar fit. He has several scars on his head from falling during fits. Myoclonic spasms are infrequent, but they have been observed occasionally, especially during sleep. He bites his tongue and frequently has involuntary micturition. His treatment has been luminal 3 gr. every night.

Mentally he is rather apathetic and lacking in concentration. His memory is slightly impaired, but his general intelligence seems fair. He is quarrelsome, impulsive and quick tempered, but shows no delusions.

PATHOLOGICAL EXAMINATION OF CASE 1.

The autopsy was carried out three and a half hours after death, and, apart from general emaciation, the external examination revealed no notable abnormalities. The left pleural sac was thickened and contained pus. The left lung exhibited an advanced stage of chronic ulcerative phthisis limited to the upper lobe, and there was an apical fibro-caseous lesion in the right lung. The heart was small and the left ventricle dilated. The myocardium was soft and flabby. There was no atheroma in the aorta. The liver presented a nutmeg appearance due to chronic venous congestion. The spleen appeared normal. Both kidneys showed evidences of chronic intestinal nephritis, the capsule being slightly thickened and adherent.

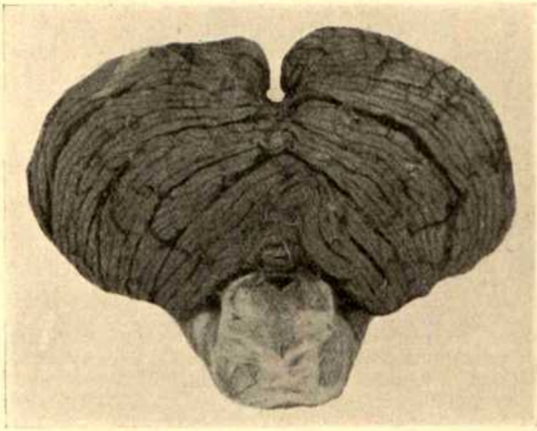

FIG. 1.—Upper surface of cerebellum, showing atrophy of the folia and widening of the sulci.

The skull-cap was normal in size and thickness and the dura mater healthy. The whole brain before section weighed 1,280 grm. The pia-arachnoid appeared slightly thickened over the vertex, but it stripped easily and without decortication. The external appearance of the cerebrum was normal apart from slight generalized atrophy of the convolutions. There was no abnormality of the circle of Willis and no appreciable arteriosclerosis. The lateral ventricles were slightly dilated, but the ependyma was healthy. The weight of the cerebrum was 1,120 grm.

The cerebellum was obviously smaller than normal, and showed marked atrophy. The weight of the brain-stem and cerebellum was 130 grm. instead of the normal 170 grm. The loss in weight of the

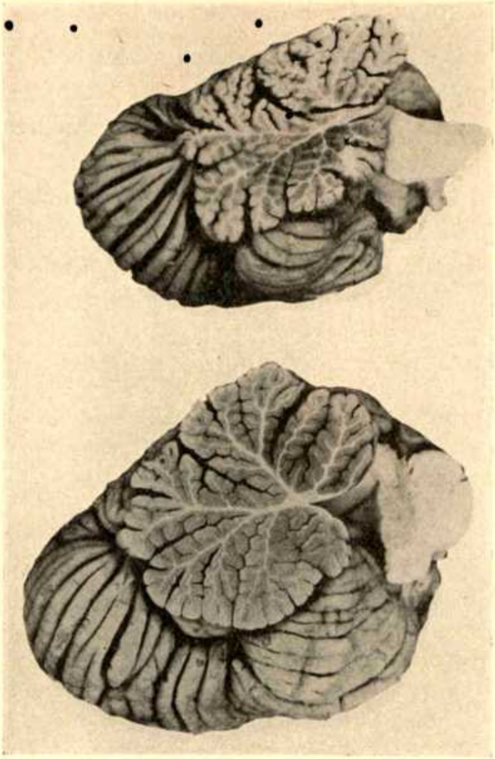

FIG. 2.—Sagittal section in the median plane of the vermis of (above) Case 1, showing atrophy of the folia, especially marked in the culmen and clivus ; and (below) an epileptic, aged 32, with approximately the same weight cerebrum. Both were photographed with the same magnification for comparison.

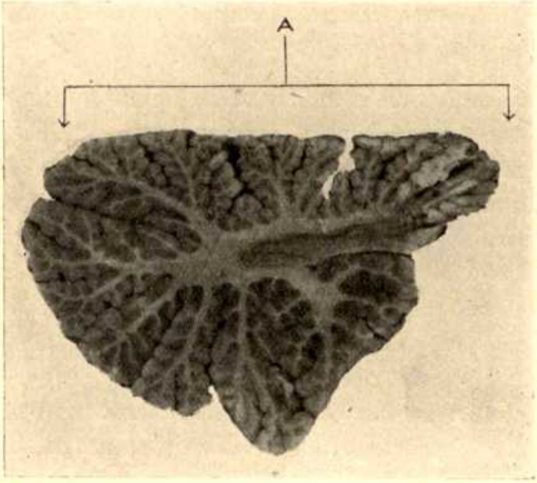

FIG. 3.—Sagittal section through the centre of the right cerebellar hemisphere, showing marked atrophy of the superior surface at A.

cerebellum may therefore be considered as approximately one-quarter. Although the cerebellum showed a general reduction in size, on closer examination it was evident that the atrophy was more marked on the anterior and superior surfaces, particularly in the superior vermis, semilunar and quadrilateral lobules, and owing to the disappearance of the normal ridge-like elevation of the superior vermis (monticulus cerebelli) the upper surface of the cerebellum was quite flat and the folia appeared shrunken and widely separated (fig. 1). On the anterior surface, there was a marked exposure of the middle peduncles as a result of the shrinkage of the folia round the great horizontal fissure. The inferior surface, on the other hand, presented a more or less normal contour, although the folia were smaller than normal (fig. 2). Palpation of the cerebellum revealed a normal consistency. The meninges appeared healthy.

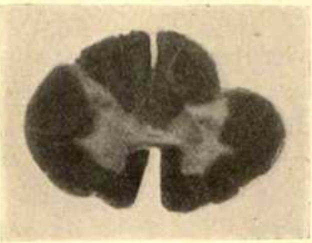

FIG. 4.—Weigert-Pal preparation of upper dorsal region of the spinal cord, showing an asymmetry of the two halves due to a deepening of the postero-lateral groove on one side. Note the distortion of the posterior root.

Sagittal sections through the vermis and lateral hemispheres further demonstrated the generalized atrophy, but with focal emphasis almost sharply limited to the folia of the upper surface of the organ (figs. 2 and 3).

The pons, medulla, and cervical cord were normal in size and shape. The dorsal region of the cord, however, was abnormally slender and presented a peculiar ribbed appearance due to a deepening of the postero-lateral grooves (fig. 4). Sections of this region of the cord showed an asymmetry due to the postero-lateral groove on one side being deeper than the other, with consequent shortening and widening of the posterior root. The lumbar region of the cord was normal in size and shape.

Histological examination.—The brain and spinal cord were fixed in formalin and pieces taken from various levels for staining by the following methods: Toluidin blue for Nissl granules; Victoria blue for fibrillar neuroglia; Bielschowsky's silver method for neurofibrils; Hæmatoxylin and scharlach R.; Weigert-Pal and Marchi methods for myelin sheaths.

Cerebellum.—Nissl sections of the superior vermis and quadrilateral lobes showed an almost complete destruction of the cells of Purkinje, a marked narrowing of the molecular layer, and a thinning of the granular layer (Plate II, fig. 5). Normal Purkinje cells could not be found in any of the sections from the upper surface of the cerebellum, for those that remained were in advanced stages of disintegration (fig. 6). In this region, the majority of the folia were absolutely devoid of Purkinje cells, but here and there one found a folium containing a few disintegrating forms, and in the latter there was a less severe affection of the molecular and granular layers.

The absence of the Purkinje cells produced a clear unstained zone giving the appearance of superficial cleavage of the outer border of the granular layer. At the junction of the molecular and granular layers, especially at the free borders of the atrophic folia, there was frequently a definite band of irregular dark-staining neuroglia nuclei (Bergmann's glial cells).

The depth of the molecular layer was reduced by a half to a third over the crests of the folia, and in some parts there was an obvious sub-pial belt of neuroglial fibres. The outer third of this layer showed a status spongiosus, and there were frequent accumulations of corpora amylacea.

The granular layer showed a marked rarefaction in addition to a reduction in depth. There was a definite loss of granule cells and a disappearance of their normal cluster arrangement. The white centres of the folia appeared normal (figs. 5 and 6).

In sections of the inferior surface of the cerebellum, there was a less severe affection of the cortex. Here the main incidence of the disease appeared to fall on the Purkinje cell layer, the molecular and granular layers presenting an almost normal appearance. The Purkinje cells were frequently normal in number but many exhibited varying degrees of degeneration from a mild chromatolysis to pale shadow forms. In several parts, however, there were large gaps in the line of cells.

Anderson's Victoria Blue method showed very little gliosis apart from slight thickening of the radial fibres of Bergmann in the molecular layer, and a narrow band of sub-pial felting at the free borders of the atrophic folia.

With Bielschowsky's method, the atrophic folia showed a crowding of the fibrils, many of which appeared to be abnormally thickened. The horizontal and radial fibrils of the molecular layer and the fibrils of the granular layer were well shown, and apparently not much reduced. The

PLATE II.

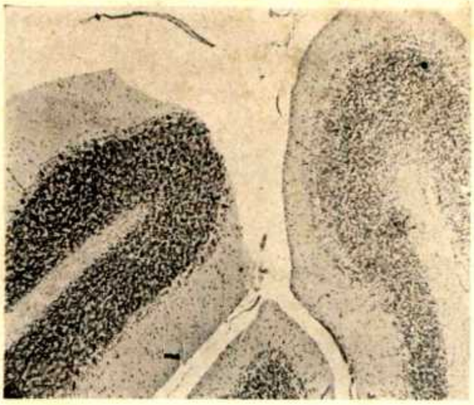

FIG. 5.

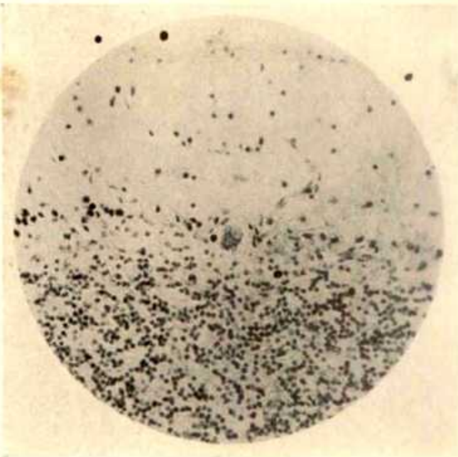

FIG. 6.

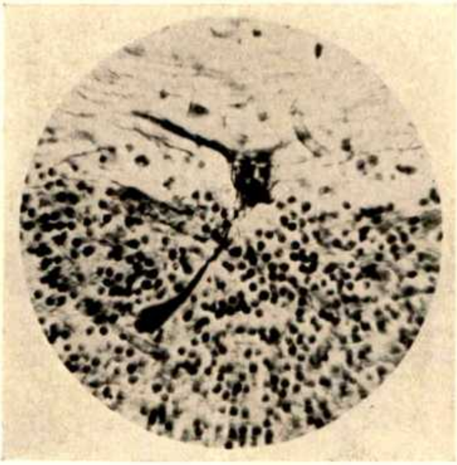

FIG. 7.

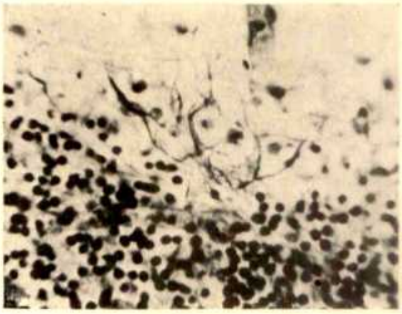

FIG. 8.

FIG. 5.—Nissl section of the superior vermis at the bottom of the sulcus post-centralis. The folium on the right is part of the culmen and shows marked atrophy of the molecular and granular layers, and disappearance of the Purkinje cells, leaving a clear zone. The folium on the left is part of the lobus centralis, and is relatively normal, but it contains only a few degenerating Purkinje cells.

FIG. 6.—Nissl section of the crest of an atrophied folium showing a belt of irregular dark-staining neuroglial nuclei in the intermediate layer. In the centre is a disintegrating Purkinje cell.

FIG. 7.—Bielschowsky preparation showing a "torpedo" or spindle-shaped swelling on the axon of a Purkinje cell.

FIG. 8.—Section of the cerebellar cortex stained by Bielschowsky's method, showing the preservation of the basket fibres and absence of Purkinje cells.

To illustrate paper by Frederick T. Thorpe.

basket fibres were also in many places well preserved, even in the most atrophic regions (fig. 8). In sections from the upper surface of the cerebellum the few remaining Purkinje cells presented a large fusiform swelling on their axons situated a short distance from the base of the cell, and in the outer third of the granular layer (fig. 7). These spindle-shaped swellings have been described by Bouman as torpedoes or "Axonschwellungen." They are almost as large as the Purkinje cell and are impregnated homogeneously with silver stain, although small vacuoles could occasionally be seen.

Sections of the upper surface stained by Weigert-Pal method revealed a distinct loss of myelinated fibres in the central white matter of the atrophic folia. The meninges and blood-vessels everywhere presented a normal appearance and no sign of an inflammatory reaction could be found. The central white substance of the hemispheres shared in the general reduction in size, with the result that there was an apparent overcrowding of nuclei, but no appreciable gliosis could be found in the Victoria Blue sections.

The cells of the corpus dentatus and roof nuclei were normal in number and size, but in the Nissl preparations the ganglion cells were pale and frequently showed an increase of lipofuchsin granules and an eccentricity of the nucleus. There was an increase of neuroglial nuclei between the ganglion cells of the dentate nuclei but no loss of fibres could be detected in the Weigert-Pal sections.

Brain-stem.—In this region very little abnormality could be detected, although sections were taken from various levels and stained by Weigert-Pal and Nissl's methods. No evidence of tract degeneration was found in the cerebellar peduncles or in the pyramidal fibres. The nerve-cells of the red nucleus, nuclei pontis and motor nuclei of the medulla all appeared healthy. The cells of the inferior and accessory olives were normal in number and size, but their cytoplasm showed no Nissl's granules and stained darkly and homogeneously, although the nuclei and nucleoli were well preserved. There was no excess of neuroglial nuclei between the nerve-cells of the olives.

Spinal cord.– Weigert-Pal, Marchi, and Nissl preparations were made from the cervical, dorsal and lumbar regions of the spinal cord. No tract degeneration could be found, and no loss of myelinated fibres in either the pyramidal or spino-cerebellar tracts. The anterior and lateral horn cells at all levels appeared normal or showed only slight chromolytic changes. The cells of Clarke's column were not reduced in number but showed marked chromatolysis. Throughout the grey column the blood-vessels appeared engorged, while here and there small capillary hæmorrhages could be seen. The spinal meninges showed no abnormality, nor could any inflammatory reaction be detected.

In all sections of the dorsal region of the cord there was a marked deepening of the postero-lateral groove on one side, at the bottom of which the posterior root appeared broadened and distorted. This produced a peculiar asymmetry of the two halves.

Cerebrum.—Nissl sections of the prefrontal lobes, the hippocampus and basal ganglia showed no abnormality. In sections of the motor cortex, however, the majority of the Betz cells were undergoing chromolytic changes and many had been reduced to pale shadow forms.

Summary.—To sum up, we have in this family of twelve members two brothers who were afflicted with the same symptoms, viz.: A typical idiopathic epilepsy followed, after a period of some years, by a gradual development of a pure cerebellar syndrome characterized by an ataxic gait, inco-ordination of movements in the upper limbs, and a slow, drawling speech.

In the case of the elder brother, epilepsy began at the age of 3, and the cerebellar symptoms at 41, but in the case of the younger brother epilepsy did not appear until the age of 19, yet the cerebellar symptoms developed at 37. There is, therefore, a marked difference in the length of time between the onset of epilepsy and the manifestations of cerebellar dysfunction in these two cases; viz., thirty-eight years in one, and eighteen years in the other.

It is difficult to decide with certainty the order in which the cerebellar symptoms appeared, as in both patients the upper and lower limbs were equally affected at the time of examination. The disturbance of gait would naturally attract more attention, and in both patients it was the first symptom to be observed.

There was no nystagmus, and no motor paralysis or sensory disturbance. The tendon reflexes were unaffected and there was no disorder of the sphincter function. Both patients presented mental disturbances which were established long before the onset of cerebellar symptoms, and were no doubt dependent upon the epilepsy.

The additional features of interest observed in the second case consisted of static tremors of the head and limbs, hypertonia during movement, and a hypometria of the upper limbs producing a typical freinage reaction.

The anatomical basis of these cerebellar symptoms was found at the autopsy of the first case to be a degenerative affection of the cerebellar cortex, and it is reasonable to assume that the same condition exists in the cerebellum of the brother now living. In the former, the duration of the cerebellar syndrome was approximately five years, when the patient died from phthisis, and the cerebellum was found to be reduced in size, and to have lost about one-quarter by weight. The folia were shrunken and atrophic, especially on the upper surface of the organ, including the superior vermis, quadrilateral and semilunar lobules.

Histologically the essential change appeared to be a primary degeneration of the Purkinje cells, starting in the laminæ of the superior surface and gradually spreading to those of the lower surface. The basket fibres were very little affected. The narrowing of the molecular layer, the rarefaction of the granular layer and the shrinkage of the white matter were apparently secondary to the disappearance of the Purkinje cells and fibres, for in the most atrophic folia all three cortical layers were equally affected, whereas in the least atrophied folia of the inferior surface the pathological process was limited to the Purkinje cells. The blood-vessels and meninges were normal.

The increase of pigment in the cells of the corpus dentatus cannot be regarded as important because such changes are common in advancing age and in this particular case there is the additional factor of the terminal toxæmia. There were no tract degenerations in either the brain-stem or spinal cord, and the mild chromolytic changes found in the cells of the inferior olives and other nuclei were in all probability due to the terminal condition. No changes of note were found in cerebral cortex and basal ganglia, apart from chromatolysis and commencing disintegration of many of the Betz cells. The asymmetry and smallness of the dorsal region of the spinal cord must be regarded as a developmental defect.

DISCUSSION.

The cerebellar syndrome.—The cerebellar lesion in the above cases may be truly described as a chronic parenchymatous degeneration of the cortex and it in no way differs from the sporadic cases which Marie, Foix and Alajouanine have called the delayed cerebellar atrophies. The predominance of the atrophy in the superior face of the organ, which was so well marked in my case, is characteristic of the whole group, and roughly corresponds to Edinger's conception of the palæo-cerebellum. Mathieu and Bertrand [6] point out that the vermis usually appears more atrophied than the lateral lobes, and suggest that this is due to the longer folia and deeper sulci of the former. The axon-swellings of the Purkinje cells are also a constant finding and would appear to indicate an early lesion of these cells. They have been well described by Bouman [7] who found them in cases of senile dementia, amaurotic family idiocy, juvenile paralysis, and Huntington's chorea. He regards them as identical with the local swellings of the neurons found by Cajal in injuries to the cerebellar cortex.

Primary parenchymatous degeneration of the cerebellar cortex is at present limited to twelve cases and these have been recently reviewed by Parker and Kernohan [8]. They were all of the non-familial type and as far as I have been able to study the literature the two cases described above appear to be the first familial cases in which the lesion is confined to the cerebellar cortex.

Holmes, however, has described four cases of cerebellar degeneration in one family, but a pathological study of one of them revealed, in addition to a typical cortical affection, a sclerosis of the inferior olives. This case has therefore been called olivo-cerebellar atrophy, although Holmes considered the olivary lesions to be secondary to that of the Purkinje cells. All four cases were very similar to mine, and there appears to be very little justification for separating them into two groups. The olivary lesion in Holmes' case could be explained by the long duration of the cerebellar symptoms, viz. 35 years, as compared with five years in my case. On the other hand, Van Bogaert and Bertrand [9] hold that the Purkinje cell degeneration is frequently a trans-synaptic extension and not necessary to the degeneration of the cerebello-petal fibres; as has been shown by cases of olivo-pontine atrophy in which the cortex is not affected. Marie, Foix and Alajouanine also regard the pure atrophies of the cerebellar cortex as separate and independent affections.

From a clinical standpoint, the cases of familial degeneration of the cerebellum differ from the sporadic forms only in their tendency to appear at an earlier age. In the twelve sporadic cases reviewed by Parker and Kernohan, the average age of onset was 62, whereas in the two cases described above the onset was at 41 and 37. In Holmes' four familial cases the onset was at 36, 38, 35 and 35 respectively, while Stone [10] has recently published a clinical report (not verified by post-mortem) of two typical cases affected at 33½ and 37, whose father and great-uncle in the first case and paternal uncle in the second case, were similarly affected at 36, 37, and 34, respectively.

The familial forms would thus appear to occur with great regularity in the fourth decade with an average age of onset at 37.

The clinical manifestations are essentially similar in the whole group of cases, viz. a gradual and insidious onset of muscular inco-ordination, involving the body symmetrically, progressing steadily and slowly over a number of years to helplessness and death from intercurrent disease. In the majority of cases the lower limbs were affected before the upper and speech became monotonous and drawling. Nystagmus is unusual but in some cases there have been nystagmoid jerks on lateral deviation of the eyes. Hypotonia is also rarely prominent, and its absence has been attributed to the slow development of the disease and the consequent influence of cerebral compensation.

In the second case described above, all voluntary movements were accompanied by a hypertonia, a phenomenon which has been observed in several of the published cases. R. Brun [11] offers an explanation of this when he states that the cerebellum may possess at the same time tonic centres and inhibitory centres working in equilibrium, the dentate and roof nuclei (tonic centres) being under the inhibitory influence of the lobes and vermis. Lesions of the dentate nucleus and superior peduncles would therefore cause hypotonia and lesions of the afferent system and cortex, hypertonia.

The olivo-ponto-cerebellar type of atrophy has already shown occational familial incidence, and it is evident that the same may be said of the pure cortical type. In fact, both conditions may be inherited as a Mendelian recessive in a manner similar to that of Friedreich's disease, which also frequently occurs in a non-familial form. There appears to be in these cases an inherited endogenous tendency to early degeneration (abiotrophy) of the cerebellar system of neurones. Such a tendency may be limited to an individual or it may occur in familial form. In the former case, it has been suggested by Marie, Foix and Alajouanine that the degeneration may be produced or precipitated by an exogenous infection, but such a history is by no means constant, and the evidence rather unconvincing.

The close association between cerebellar atrophy and Friedreich's disease is borne out by the presence of a slender and asymmetrical cord in the first patient. Similar developmental defects are not infrequently found in Friedreich's disease.

THE RELATIONSHIP BETWEEN CEREBELLAR ATROPHY AND EPILEPSY.

The two cases of cerebellar atrophy described above are somewhat unique in the fact that they were the only two members of the family suffering from epilepsy. At first sight it might appear that the cerebellar atrophy was in some way specially connected with the occurrence of epileptic fits. There is, indeed, abundant evidence to show that epileptic fits frequently produce degenerative changes in the cerebellar cortex.

Spielmeyer [12] has devoted much attention to this question, and has discovered characteristic cell degenerations in the cornu ammonis and cerebellum in as many as 80 per cent. of epileptic brains. He regards the changes in the cerebellum as similar in principle and also as frequent as those of Ammon's horn. These consist of scleroses—a proliferation of the neuroglia in the molecular layer, which replaces the degenerated nervous tissue substance and, above all, the loss of Purkinje cells. He also suggests that these changes are related to the mechanical factor responsible for the seizures; i.e., they are ischæmic changes resulting from angiospastic constriction. Spielmeyer believes that the cornu ammonis and the Purkinje cell layer of the cerebellum have a relatively unsatisfactory local blood supply, and are therefore peculiarly sensitive to any partial hindrance to the circulation. In this respect Uchimura [13] has demonstrated that vessels in these areas are unusually long and tortuous, and that the capillary network is less abundant than in other parts of the brain.

It would appear, therefore, that secondary degenerative changes in the cerebellar cortex are a common occurrence in idiopathic epilepsy. But such changes consist of focal areas of atrophy and sclerosis, and are rarely severe enough to produce clinical symptoms. They are of a different order to the widespread diffuse and symmetrical atrophy found in the group of primary degenerations of the cerebellum, of which the case above described is a typical example.

On the other hand, degenerative lesions of the cerebellum with clinical manifestations have been found in cases of myoclonus epilepsy. Such cases have been recorded by Haenel-Bielschowsky [14] and Ramsay Hunt. The latter author reports four sporadic cases of epilepsy and myoclonus which also showed signs of cerebellar dysfunction, consisting of generalized intention tremors, scanning speech, dysmetria, dysdiadochokinesia, hypotonia and asthenia. Unfortunately the anatomical basis of their cerebellar symptoms could not be ascertained, but a histological study of a similar case associated with Friedreich's disease suggested that a "primary atrophy of the dentate system" was responsible.

It is evident, therefore, that primary cerebellar atrophy occasionally occurs in subjects of myoclonus and epilepsy. In the two cases I have described there was a long-standing epilepsy, but no myoclonus. The epilepsy and cerebellar symptoms may be considered as manifestations of two distinct disorders in the same individual, for, as pointed out by Ramsay Hunt, combined forms of the various congenital, familial and hereditary types of nervous disease are by no means uncommon. Many such instances have been described by Jendrassik [15]. The combination of epilepsy and Friedreich's disease excites little comment, but in view of Spielmeyer's researches the occurrence of a cortical cerebellar atrophy in an epileptic is of special interest and suggests the possibility of a closer pathological association between these two conditions.

RÉSUMÉ.

A familial form of primary parenchymatous atrophy of the cerebellar cortex is described, in which two brothers, at the ages of 41 and 37 respectively, developed a progressive ataxia of legs and arms, and a slow drawling speech. The anatomical basis of these symptoms was ascertained in one of them after a duration of five years, and was found to be a pure cortical type of cerebellar atrophy. The cerebellum was reduced in size by approximately one quarter, and showed a generalized symmetrical atrophy with marked emphasis on the upper and anterior surface, especially the superior vermis and quadrilateral lobes. Histologically, the essential lesion was a diffuse destruction of the cells of Purkinje. This particular type of atrophy has heretofore only been described in non-familial cases, unless one includes the Holmes family of four cases, of which the only one examined histologically revealed an olivo-cerebellar atrophy.

Familial degeneration of the cerebellum occurs more often in males, and the onset is between the ages of 32 and 41, whereas non-familial forms tend to occur at a much later age. Both forms are assumed to be due to an endogenous degenerative process or abiotrophy, but in the sporadic cases there may be an additional exogenous infective or toxic factor.

The frequent combination of cerebellar atrophy and lesions of the spinal cord is mentioned, and in the case described a developmental defect of the cord was found, which suggests a latent association with Friedreich's disease.

The two patients described were subject to epileptic seizures which had been present for thirty-eight and eighteen years before the onset of cerebellar ataxia. The cerebellar lesion, however, was not the focal ischæmic type which Spielmeyer finds in most epileptic brains, but a gross generalized atrophy typical of the primary degenerations.

The association of cerebellar atrophy and epilepsy in these two cases is regarded as accidental, and merely represents the not uncommon occurrence of a predisposition to two independent nervous disorders in one individual.

I wish to express my thanks to Professor A. J. Hall for his helpful advice and criticism; and to Dr. Arthur Pool, the Medical Superintendent of the South Yorkshire Mental Hospital, for permission to publish these cases.

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THE FRONTAL LOBE IN MAN: A CLINICAL STUDY OF MAXIMUM REMOVALS.[1]

BY WILDER PENFIELD AND JOSEPH EVANS,
Montreal.

REMOVAL of very large areas of the human brain in neurosurgical practice offers an opportunity for detailed neurological study, especially in the occasional case which fortuitously presents many of the conditions which would be demanded of a physiological experiment. Three cases of radical removal of large portions of one frontal lobe have been selected for this communication because of unusual opportunity for study before and after operation and because the excised portions of the brain could be accurately examined.

Advance in knowledge of the functions of the frontal lobes is difficult to secure because of the fact that substitution of one cerebral region for another is no doubt possible, and there may well be bilateral representation of many cerebral processes which take place in this *terra incognita.* Furthermore, animal experimentation can contribute little, as all animals, even the anthropoids, possess but rudimentary prefrontal development and it is impossible to explore the finer thought processes of speechless animals.

Extirpation of a tumour, however radically carried out, does not provide a perfectly satisfactory subject for study, as tumours often displace cerebral tissue to a great extent without destroying the tissue or its function. The only tumour cases which are acceptable for investigation are those in which an infiltrating neoplasm has made it advisable to resect a large block including brain and tumour. The cases, however, which are most useful for our present purpose are those of patients suffering from chronic epilepsy due to a focal lesion of such a type and situation that lobe amputation offers the only hope of relief from the seizures.

Case 1.—R. I., R.V.H. Right frontal extirpation; calcified oligodendroglioma.

This case offers an unusual opportunity in that the patient was observed closely from childhood onward and the removal was radical. The patient was

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43 years of age. Occasional "splitting" headaches began at the age of 14. At the age of 20 there was a Jacksonian seizure. This was followed by a series of such seizures at 28 years of age and another at 33, at 34 and at 40 years. From 40 to 43 years of age, when operation was carried out, there were occasional small Jacksonian attacks.

Dr. Colin Russel, who examined her for us on her arrival in Montreal in November, 1928, found bilateral papillœdema, left plantar extension, comparative weakness of the left arm and leg, and he made the observation that she was "mentally not up to her own standard in looking after household arrangements."

A right frontal osteoplastic craniotomy was carried out by one of us (W. P.) and a large, partially calcified oligodendroglioma was exposed. It infiltrated the frontal lobe but did not involve the anterior pole. Tumour and lobe, except for precentral gyrus, were resected *en bloc*. Fig. 1 indicates the extent of removal as it appeared to the artist who was present at operation.

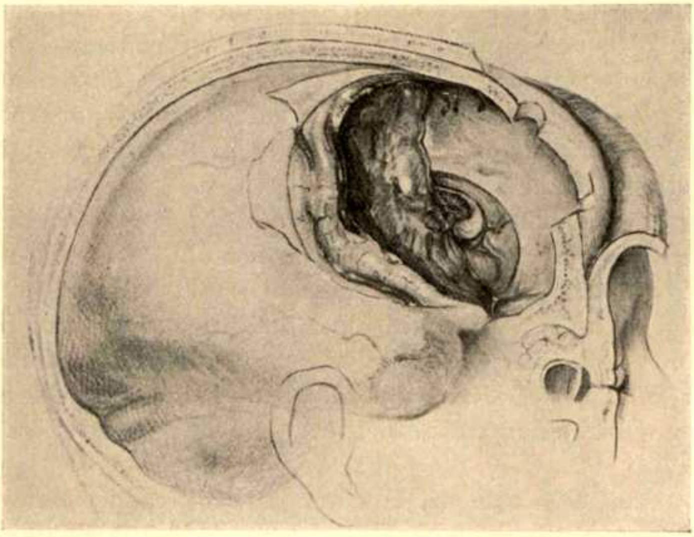

FIG. 1.—Operative sketch showing the extent of the removal in Case 1. This is the unprompted conception of the artist who was present at the operation.

It is always difficult when dealing with an expanding lesion to know how much the cerebral tissue has been rarefied and displaced without being rendered functionless. Therefore we have indicated in fig. 2 our conception of the site of removal by the continuous line to which the arrows point. An infiltrating tumour does not displace brain to the same extent that a slowly growing encapsulated one does, but it does displace it somewhat so that the line of crosses in the same figure gives an estimate of the cerebral tissue actually destroyed which is safely conservative.

The operation was carried out under local anæsthesia. She may have lost consciousness for a short time when there was a sharp hæmorrhage, but she was otherwise alert during the procedure, spoke to the operator frequently and talked intelligently about her children, her chief preoccupation. At the end of six hours of this operative ordeal she apologized for having made so much trouble !

That night she slept at long intervals. Twice during convalescence she was catheterized, but otherwise recovery was entirely uneventful and she was out of bed in two weeks. Neurological examination on discharge was entirely negative although she was not subjected to so searching a sensory examination as the next case. Two months after operation she had returned to her own family and during the year which followed lived a happy and essentially normal life as will be described in the discussion to follow.

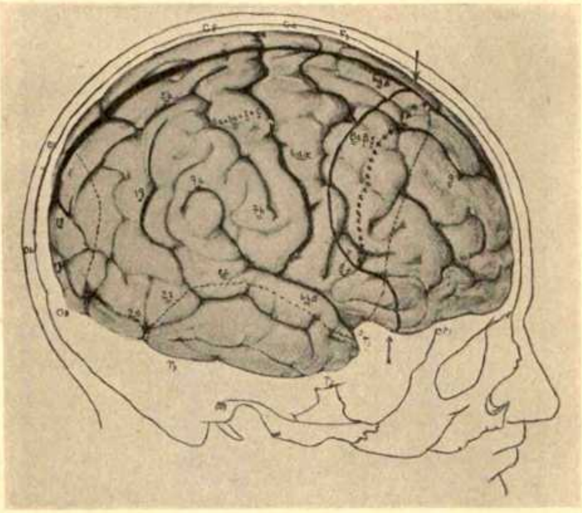

FIG. 2.—*Case* 1. The solid line indicates the line of removal ; the crosses indicate a more conservative estimate of the cerebral tissue actually removed if the displacement which the tumour may have produced be considered.

My instinctive reaction (W.P.) was to withhold this case from publication. The patient was my only sister. But the close bond of sympathy that had existed between us for many years makes it possible for me to evaluate the effect of the loss of the frontal lobe upon her personality and her mental capacity. My opinion at all events must be interpreted in the light of this personal relationship and if she were alive I am sure she would approve of such an analysis in the hope that it might help others.

After this case had been presented before the Association for Research in Nervous and Mental Disease the following letter was received from Professor Russel, which is now printed in full as it expresses his opinion of the case.

" Because of my great interest in her I would have liked to contribute to he discussion of the condition of your sister following lobectomy. You will remember that I sat and talked to her during the operation and left her only at about 5 o'clock when you were cleaning up. You showed me how much of the anterior lobe had been removed, and one could see in the midline the falx perfectly clean.

"I dropped in to see her between 8 and 8.30 that evening and although she was somewhat nauseated and had been vomiting, probably the result of the local anæsthetic, she expressed her appreciation of what she considered my kindness in giving up my time, so perfectly and with so much courtesy that it was really very impressive. She said that she had felt so afraid of causing you distress by making an exhibition of herself and that I had helped her. When I remarked that the only exhibition I had seen was one of the best exhibitions of courage that it had been my fortune to witness, she expressed her gratitude so nicely that one could not help wondering how much the frontal lobe had to do with the higher association processes. Of course, as you have already said, it is not so much the frontal lobe as a slow growing tumour that involved the frontal lobe, and probably the function of that lobe had been gradually taken on by other parts of the brain.

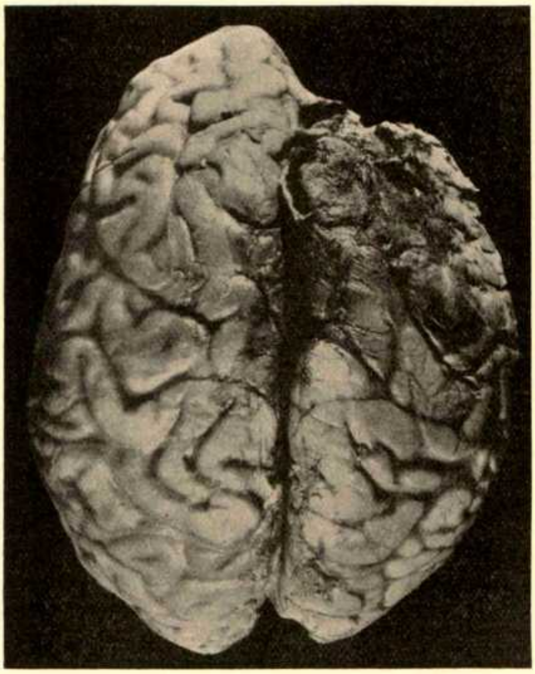

FIG. 3.—The brain of Case 1 as seen at autopsy, two years and five months after the operation of figs. 1 and 2. The anterior portion of the amputated pole is recurrent neoplasm.

"During her convalescence I so often would get her to discuss books that she had read, and her memory was so good, and she showed such good judgment in her criticisms that I cannot help but feel that her feeling of inadequacy explained in her letter to you when she asked for some means of sharpening up her intelligence might very well be explained by the fact that she had been a very conscientious mother of several children who had neglected her social contacts on account of her domestic duties, and was feeling the lack of facility in social intercourse. It is not an uncommon experience under such circumstances."

Her condition following operation will be taken up in detail in the discussion to follow.

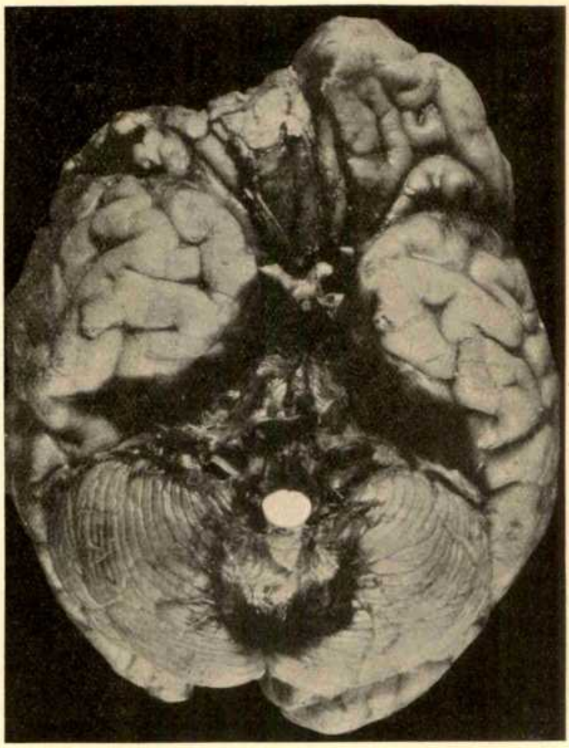

FIG. 4.—The same brain as fig. 3, seen from below.

Twenty-two months later, following a rather sudden reappearance of symptoms, she was re-operated upon at our request by Dr. Harvey Cushing who found a recurrence of the tumour and removed it again without any further amputation of cerebral tissue. She continued to feel well but six months later died from hæmorrhage into the tumour and autopsy again showed neoplastic recurrence. Thanks to the kindness of Dr. Carl Rand of Los Angeles, who performed an autopsy, we can show a photograph of her brain (figs. 3 and 4). It will be seen in fig. 3 that there is sufficient regrowth of the tumour to make the hemisphere appear about 3 to 5 cm. longer than it really was. Re-growth of such a tumour not infrequently simulates brain in form.

Complete examination of the brain showed that there was no neoplasm nor abnormality elsewhere. The case will be taken up again under the heading of general discussion.

Case 2.—W. B., R.V.H. Left frontal lobectomy. Post-traumatic epilepsy, cerebral cicatrix.

At 16 years of age he fell from a scaffolding and received a depressed fracture of the right frontal region. He was unconscious for two and one-half weeks. He left the hospital in two months and felt "all right" except that his memory did not seem as good as formerly. He did not work for a year, at the end of which time he took a position as caretaker of a skating rink, a position he continued to hold until recently. At the age of 22, epileptiform seizures of the frontal lobe type made their appearance as described elsewhere.[1]

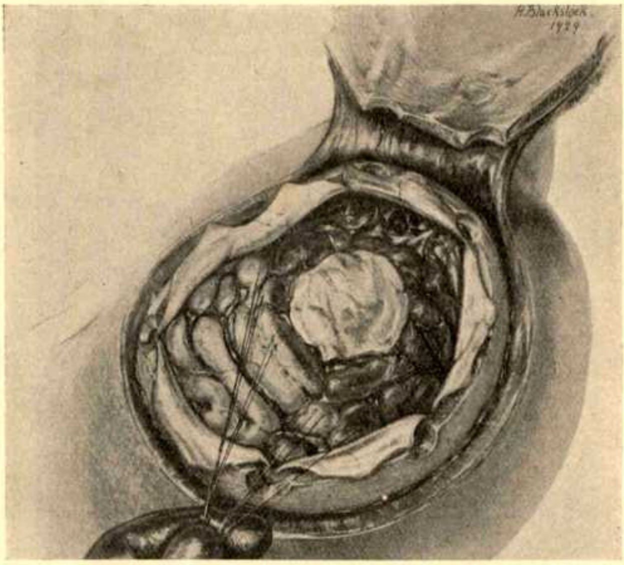

FIG. 5.—Sketch of the lesion exposed at operation in Case 2, showing the sclerosed and atrophic frontal pole and the meningeal adhesions.

Two years later encephalography demonstrated enlargement of the anterior horn of the left lateral ventricle, a cyst in the left frontal lobe and migration of the third ventricle toward that side. Osteoplastic craniotomy was carried out (November, 1929). It revealed abnormal, leathery frontal convolutions and dense dural adhesions (fig. 5). Amputation was carried out through normal tissue as indicated by the cutting threads in fig. 5 (see also fig. 6). Incision was made directly inward to the wall of the ventricle. The plane of excision was then sloped somewhat forward so that at the falx the removal was about as far anterior as the end of the ventricle. The line of removal as seen on the surface is indicated in fig. 7.

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[1] Penfield, W., and Gage, L. "Cerebral Localization of Epileptic Manifestations." *Arch. Neurol. and Psychiat*, **30**, 709, 1933.

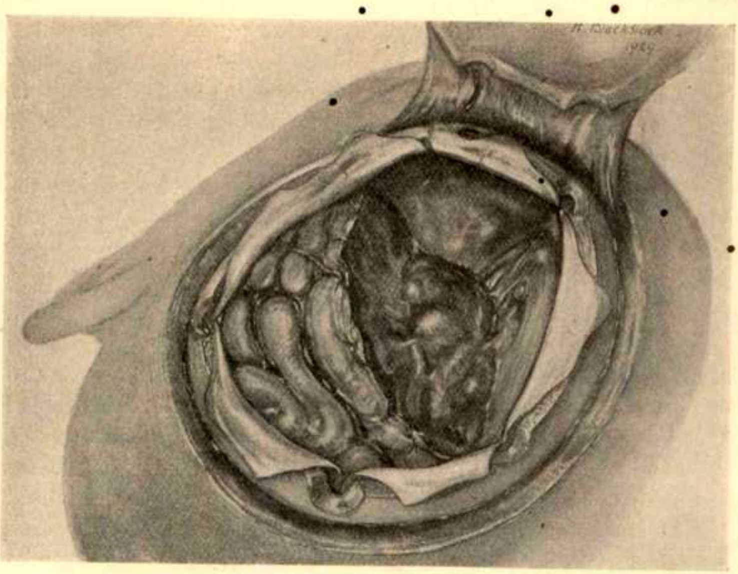

FIG. 6.—The artist's conception of the extent of the lobe amputation in Case 2.

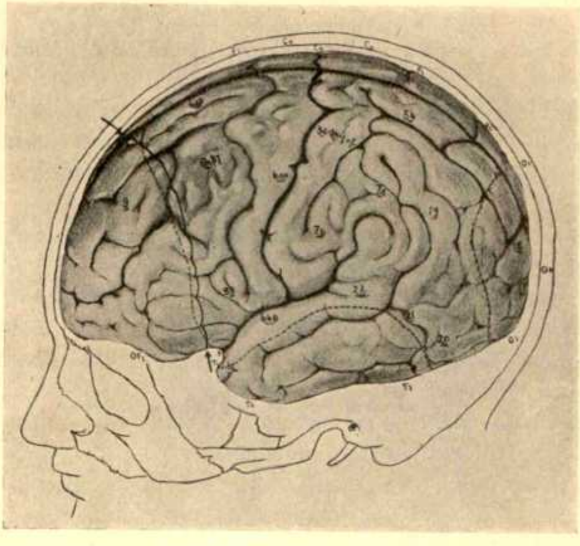

FIG. 7.—Surface projection of the amputation done in Case 2. The traction of the huge scar probably pulled the whole hemisphere forward so that the line of removal should be placed farther posterior.

During the operation, which was done under local analgesia, the patient was able to talk with us intelligently. Following it, at midnight, he was mentally clear but did not remember about the operation nor did he seem to recall recent events. In the first week after operation he became disorientated and somewhat confused mentally and developed a hemiparesis. He had difficulty in finding words.

One week after operation he had become well orientated for place and partially for time. Memory, however, was still deficient as far as recent events were concerned. The hemiparesis was improving. Two weeks after operation he was much clearer; he seemed slow but remembered recent and past events fairly well and could do simple arithmetical sums but not difficult ones, and the hemiparesis had disappeared.

Six months after operation the patient's physical examination showed him to be normal and he had returned to his former occupation. He reported that he was able to think better, act more quickly and that he was less irritable and quarrelsome than before operation. This should not be taken to mean that we consider frontal lobectomy would benefit a normal individual. The improvement over his former condition which continues up to the present time (five years later) is, of course, due to the complete arrest of his epileptiform seizures.

It is not wise to compare the man too closely with himself as he was before operation, because of the disappearance of the epilepsy. We can only study him objectively and in the light of the promise which he gave at the age of 16 before the accident.

Psychological examinations.—Dr. David Slight has examined the patient on several occasions and we here quote from his notes.

February 6, 1929 (two and a half months after operation): "General manner and appearance normal. When seen before leaving the Hospital the patient gave the impression of what can only be described as being 'blank' or 'out of touch.' Orientation good for time, place and person. On leaving Hospital he was distinctly hazy about time, but he has had no lapses in the past month.

"*Stream of thought*: Rate normal, flow coherent and logical. Denies any periods of confusion or dreaminess.

"*Emotional status*: Bright and consistently so. For a time after leaving the Hospital he was distinctly irritable, being upset over minor things, but he is now controlled and balanced. Denies any periods of depression or other fluctuations in emotional state.

"*Mental content*: No delusions, hallucinations or other abnormal phenomena. Memory is good, both for immediate and past events with the exception of a period of amnesia extending over much of the time in Hospital. For example, he can relate what he had for supper last night and also incidents at a theatrical show he attended a week ago. He can repeat six digits forward and five backwards. (One might claim that this is slightly below par since the average adult is expected to repeat six digits backwards, and the fourteen year old level to repeat seven digits forward.) Intellect is good and he tests up to the fourteen year old level according to the Binet-Simon scale. Judgment and insight appear good.

"*Conduct*: No abnormalities so far as can be gathered. He apparently occupies himself in a normal fashion, reads the paper, goes out, and as already stated, attended a show last week. Writing and speech are normal.

"To sum up: It would appear that the patient shows no demonstrable mental change at the present time, and to judge from his previous occupation and other information it would seem that there is no mental loss. This is said with the reservation that any tests or judgments relate to what may be called a static condition, and do not entitle one to pass judgment on the patient in what may be called the dynamic situation."

Following a later examination (December 22nd, 1932, four years after operation) Dr. Slight again reported: "The patient was co-operative during the examination and gave a good account of himself. He is apparently free from any subjective sensations and has no complaints to make regarding his ability to live and behave in a normal way. Clinical examination of his mental state does not show any apparent indications of abnormality, and if one were not aware of the previous surgical procedures one would probably pass him without particular comment. On further questioning he does acknowledge one difficulty, and that is in regard to processes of mental arithmetic such as are involved in playing cards, and he particularly mentions a game called 'Five Hundred.' He is apparently unable to add figures together mentally and finds it necessary to use paper.

"Although his memory span tests up to the average adult level, a Binet-Simon examination made through the courtesy of Dr. W. T. B. Mitchell shows that on the Stanford revision of the Binet-Simon he has a mental age of 12 years and 4 months, with an intelligence quotient of 82. During this examination it was noted that he showed an apparent fatiguability and that there was a 'scatter' in the test. On the Healey completion test No. 2 he had a score of 73; 66 being regarded as the average level. The Healey completion 'B' test was completed in 45 seconds and 14 moves, which gives him a performance level of seventeen years.

"One point interesting and worthy of note is his spontaneous statement that emotionally he feels much more controlled now than in the past. He states that previously he was very antagonistic toward people and toward religious topics and such like, whereas now he finds himself more controlled in approaching and discussing such matters."

Vestibular reactions: Before operation the following examination was recorded in the Outpatient Clinic of the Department of Otolaryngology:

"February 7, 1928: Hearing losses of middle ear variety. Cold caloric test of both ears reveals normal response from each ear with 4 c.c. of ice-cold water. Both internal ears would seem to be normal but there is a hearing loss from the healed middle ear disease."

Six months after operation he was examined by Dr. W. J. McNally, who made the following note (May 10, 1929): " Cold caloric test : Right ear : Four c.c. ice-cold water elicits a response of nystagmus from the horizontal canal—no response from the vertical canal, i.e. when head is erect; no dizziness. Ten c.c. of water at 120° F. elicits a few nystagmoid movements from the right horizontal canal. No response from the vertical canal, or very weak response.

" Left ear : Four c.c. ice-cold water—no response from either vertical or horizontal canal. Ten c.c. water at 120° F. elicits a definite nystagmus from the horizontal canal sharper than from the other ear; no response from the vertical canal. Ten c.c. of ice-cold water in the right and left ear produces a response from both the horizontal and vertical canals, but it is definitely diminished. This may be due to thickening of the drums from previous middle ear disease. There is no dizziness from any irrigation.

" Impression : Suggestion of diminished irritability of both internal ears, more marked in the vertical canals. There is a weakly positive de Kleijn sign from the left cerebral hemisphere. There is a long history of previous middle ear disease which has interfered with hearing."

Four years after operation Dr. McNally made a second note (December 7, 1932) : " The right ear drum is thickened, milky white, intact. The left drum is thickened, milky white and shows scar in the postero-superior quadrant. No spontaneous eye nystagmus. While standing the patient is not disturbed by placing the head in any position nor is he disturbed or over-balanced by any sudden passive movement of the head or shoulders.

" Two and one half c.c. of ice-cold water in the left ear elicits a prompt nystagmus normal in character from the vertical and horizontal semicircular canals of that side. The duration of the nystagmus is quite short, about one minute. There is no dizziness. Two and one half c.c. of ice-cold water in right ear elicits the same normal response as above except that it is slightly less marked. In both cases the response from horizontal canals was more marked than from vertical canals. Ten c.c. at 120° F. in the right ear elicits prompt nystagmus from the horizontal and vertical canals, but definitely less marked when compared with the opposite side."

Dr. McNally summed up the vestibular examinations : " In other words there is no evidence that the quick phase of nystagmus shows any exaggeration toward the side of the lesion (de Kleijn's sign of a cerebral hemisphere lesion). If anything, this patient shows more response when the quick phase of nystagmus is to the opposite side of the lesion. When one considers the thickness of the drum one must conclude that both labyrinths are responding normally to stimulation.

" In the wheel chair with head erect (horizontal canals) normal response after ten turns to either side; no dizziness. It is worthy of note that after the caloric stimulation and rotation tests there was never at any time the slightest dizziness or past-pointing in spite of the fact that the other objective signs of labyrinthine stimulation were quite normal. I do not know quite what the significance of this fact may be."

Special sensory examination. November 28, 1932.

(*A*) *Spontaneous sensation.*—He has had no pain, numbness or tingling in the extremities, nor is there any lack of recognition of the position of the limbs. No paraesthesia of any nature.

(*B*) *Objective study.*

Light touch.—Recognition of cotton wool entirely normal, over the ulnar and radial sides of the forearms and over the lower limbs. Tactile acuity as tested with the von Frey hair is normal over the ulnar and radial borders of the arms, over the lower legs and also over the dorsi of the feet.

Pressure touch.—Not tested.

Localization.—Errors in centimetres. Ten trials.

Points tested on the right forearm and indicated by the left index finger	1·4	1·8	0·8	0·6	1·6	2·0	1·0	1·3	2·0	1·8	Average 1·4 cm.
Left forearm indicated by right index finger.	2·0	1·5	2·0	0·6	1·6	3·0	1·0	1·0	1·5	1·0	Average 1·5 cm.
Right leg indicated with right index finger.	2·0	0·5	0·8	2·8	1·5	0·5	2·5	1·5	3·2	4·0	Average 1·9 cm.
Left leg indicated with left forefinger.	0·7	2·7	0·3	1·0	2·0	1·5	1·7	0	0·3	0	Average 1·0 cm.

Roughness.—Not tested with the Graham Brown esthesiometer, but three grades of sandpaper were used, No. 2, No. ½, and the reverse or smooth side of either of these called 0. Recognition of these various grades of sandpaper, interchanged, was quite normal over all the fingers, except for a slight confusion in the right fifth and also in the third left. There were no gross abnormalities in the skin, because of which there might be expected abnormal sensation. In any event these changes were very slight and may well not be significant.

Tickling and scraping.—Normal over the palms of both hands, over the soles of the feet. Cotton wool tickling and scraping were all normal.

Vibration.—Tested over the nails of the first and fifth fingers and the first and fifth toes and was quite normal.

Compass test.—Equally accurate on thenar and hypothenar regions of the two hands.

Pain.—(*a*) Superficial pain: Pinprick recognized normally over the lower arms and over the radial and ulnar borders of the hands, also over the lower legs and dorsi of the feet. (*b*) Pressure pain: This was tested in the forearms, in the upper third between the radius and ulna. Pain was recognized at 7 kgm. on the right side and at 7½ kgm. on the left. In the legs the testing was done in the medial portion of the calf. On the right pain was recognized at 10 kgm. pressure; on the left at 8½ kgm.

Temperature.—Differences of 27 and 34 degrees and 29 and 30 degrees were recognized over the lower extremities and over the forearms. A temperature difference of 29 and 29½ degrees could not be differentiated.

Position.—Imitation of the position of one extremity by the other was prompt and accurate.

Passive movement.—Three to five degrees of movement were recognized in the fingers and in the toes accurately and without hesitation. No falling away of the unsupported upper limbs when the eyes were closed; lower extremities not tested.

Active movement.—(See above).

Weight.—Right hand supported able to differentiate between 100 and 105 grm. of weight and the left hand able to do the same. The right hand unsupported differentiated between 105 and 120 grm., 110 and 120 grm., and on one occasion between 100 and 105 grm., though on a second trial 100 to 105 grm. were called about the same. Left hand unsupported not able to differentiate between 100 and 105 grm., nor between 110 and 120 grm., but the difference between 105 and 120 grm. was recognized.

Size.—This was tested in the hands by the use of test tubes of the following diameters: 1·1, 1·6, 1·7 and 2 cm. The two middle tubes were confused rather readily but this was within normal limits.

Shape.—Triangle recognized in both hands promptly.

Form.—Calipers, two-point compass and throat sticks were all recognized readily.

Texture.—Cotton wool, paper and a rough towel all correctly named.

Consistency.—Hard rubber tip recognized as such. Thermometer bulb recognized as hard and cotton recognized as soft.

Figure writing.—

Left palm :—										
Written	7	4	3	2	1	6	8	9	0	5
Called	2	4	3	?	1	6	8	9	8	5
Also left palm :—										
Written	5	7	2	3	6	1	9	0	8	
Called	5	7	2	3	6	1	9	0	8	
Right palm :— (four trials)										
Written	5	7	2	3	6	1	9	0	8	
Called	5	7	2	3	5	5	5	0	8	
	5	7	2	3	6	5	9	9	8	
	5	7	2	3	8	1	9	0	8	
	2	7	2	3	6	1	9	8	8	

Summary of Findings on Sensory Examination.

(1) Suggestive error in spot finding on the right leg as indicated with the right index finger.

(2) Slight unexplained error in recognition of grades of sandpaper fifth finger right and third finger left.

(3) Left hand unsupported recognized the differences in weight less readily than the right.

(4) There seems to be definitely diminished acuity in recognition of figure writing in the right palm. This is irrespective of radial or ulnar border.

Summary of Objective Examination.

The defects which we were able to detect in this case were as follows:—

(*a*) Small errors in sensory examination which are probably negligible, i.e., in spot-finding in right leg, in figure-writing with the right hand and in weight differentiation with the left hand.

(*b*) Unexplained absence of dizziness and past-pointing after caloric and rotation stimulation although both labyrinths respond normally to stimulation. De Kleijn's sign of a cerebral hemisphere lesion was absent.

(*c*) Subjective decrease in capacity for mental arithmetic and bridge playing. Mental age of 12 years and 4 months with an intelligence quotient of 82 by Stanford revision of Binet-Simon test. Completion level of seventeen years in Healey completion test.

(*d*) Some lack of initiative. See discussion to follow.

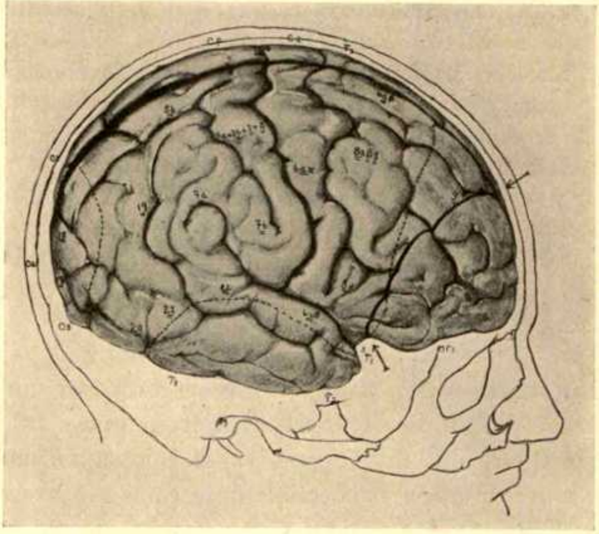

FIG. 8.—Surface projection of the removal carried out in Case 3. There was much traction here also as in Case 2.

Case 3.—G. G., R.V.H. Right frontal lobectomy. Post-traumatic epilepsy, cerebral cicatrix.

This boy of 19 years received a severe head injury at the age of 8 and was referred by Dr. Colin Russel. Epileptiform seizures of right frontal lobe type had been present for one year. In November, 1931, a right frontal osteoplastic craniotomy was performed. Three cysts were found in the frontal pole and radical excision was carried out as indicated in fig. 8, cutting across the anterior end of the ventricle. The excised tissue, after evacuation of the cysts, weighed 34 grm.

There was a post-operative hæmorrhage which necessitated re-operation on the second day. Otherwise the recovery was uneventful, neurological examination was negative on discharge and he has had no recurrence of the epileptic seizures up to the present, three years later.

One year after operation, in December, 1932, he was examined with the following results:—

(1) Special sensory tests similar to those in Case 2 above were entirely negative.

(2) Audiographic and vestibular tests by Dr. Scott-Moncrieff were entirely normal.

(3) Psychometric examinations by Dr. David Slight may be summarized as follows:—

" He shows no apparent psychiatric difficulty. He appears to have adjusted well to work and has on several occasions been able to give public demonstrations of his firm's products in a large store.

" Since being at home he has continued to play such games as cards and tennis, and he has actually continued playing with a basketball team. It is said that there is no loss of ability in these games. In so far as reading, writing and arithmetic processes are concerned there is no apparent loss of function. His memory span is 8 digits forward and 6 backward. He appears to be interested in his work and has ambitions to make progress, hoping and planning to take up studies to further his work."

In summary the excision in this case was smaller than in the two former cases. The portion of brain removed was doubtless partially incapacitated before removal. Physical and psychological examinations reveal no defects.

Discussion.

It may be urged that to destroy a delicate instrument is not the best way of studying its function. But we have recorded in some detail the results of three frontal removals selected from many other available cases because of their suitability for study. It is always difficult to assess the value of the information from clinical cases as we are not carrying out experiments on normal patients, but, rather, desperate operations upon patients in the brain of each of whom there was abnormality to begin with. With these criticisms in mind the cases presented still seem to offer an opportunity of making deductions of value with regard to the frontal lobe, deductions both positive and negative.

It is evident that removal of large portions of the brain may be carried out without even temporary loss of consciousness. The vestibular reactions were normal in the two cases carefully examined. But in the large left frontal removal (Case 2) there was unexplained absence of dizziness and past-pointing after caloric and rotary stimulation. This defect was not present in the smaller removal (Case 3) and was not tested for in Case 1.

The removal of left frontal lobe in Case 2 had been carried out in this case back to within one or two centimetres anterior to the precentral gyrus. In its lower extent the line of removal crossed Broca's convolution not far from the anterior end of the fissure of Sylvius. At the base of the hemisphere the removal skirted closely the posterior edge of the orbital plate and lesser wing of the sphenoid. Mesially the plane of removal was more anterior than laterally.

Aphasia in this man did not develop immediately and disappeared within three weeks, leaving behind no difficulty in speech whatever. The disturbance of speech was therefore attributable to transient neighbourhood change in cerebral structures which had not been removed. Special psychological tests record a normal level for a man of his limited education. He showed at no time reflex forced grasping.

What defects has he? He, himself, is conscious of only one unfavourable sequel to operation, that is difficulty in performing mental arithmetic and in playing bridge (a game which calls, no doubt, for a certain limited type of memorization and computation!). If he can write the figures down and see them he says he can do his arithmetic. But even after five years he cannot summon the figures and add or subtract them in his head as easily as formerly. That ability seems to have been partially removed with the amputation.

Is there anything else lacking in this man, perhaps lacking since the original laceration of his frontal lobe? His mother praises him as being docile at home, but admits that he may have shown too little initiative ever since his injury. His father is head groundsman for McGill University, the son having worked under him for two years before operation and for more than a year afterwards, was laid off only along with others at the time of a general "cut." The father states that as a workman he never had a better helper, "but," he added, "he never had a job that I didn't get for him." He should have added "since the accident," for it may be recalled that this patient had had enough initiative at the age of 16 to find his way to England, and had secured himself a job there.

To sum up: this patient is a likeable fellow, a good workman and a useful citizen. It is quite certain he will never be a revolutionist. He has lost something that psychometric examination does not evaluate. He has lost initiative; not all of it, but much of it.

The extirpation of the right frontal lobe in Case 1 was the largest of the three removals, and may be discussed at greater length. To recall the details, this was the case of a woman of 43 whose lobe contained a calcified oligodendroglioma and whose amputation was carried back to within a centimetre of the motor gyrus all the way down to the lowest frontal gyrus. From this line it passed across cleanly to the mid-line so that the septum pellucidum and the anterior two or three centimetres of the sectioned corpus callosum were visible after the removal (fig. 1).

To judge what this patient had lost by being deprived of nearly all of her right frontal lobe demands that an estimate be made of what she would have been had she had a normal right frontal lobe at that age. Because one of us (W. P.) had known her intimately from childhood we believe it is possible to evaluate the mental and personal changes. This we have undertaken at all events.

The history was long. For twenty-three years before operation there were Jacksonian seizures at very long intervals, which indicates that the oligodendroglioma was probably present for that length of time, an increase in the rate of growth doubtless occurring towards the end. The removal was of lobe and tumour, not of tumour alone. This was borne out by the post-mortem examination, which also showed that other areas of the brain were normal.

The rapid recovery and relief from the symptoms of compression do not concern us. The fact of the compression renders a comparison of her state immediately before operation with that afterward of no value. Such comparison would, of course, show only improvement. The analysis must go back to a much earlier period.

After operation she resumed her duties as wife and the mother of six children with greatly increased efficiency. But she was conscious of not being quite as alert mentally as she should be. This is best expressed in her own words. In July, 1929, seven months after operation, she wrote:—

> "Dr. Taylor asked me if I felt that mental activity was improving, and I said 'Yes,' but it seems as though each time I feel encouraged that way I do a series of very stupid things. Perhaps it is just a case of 'pride goeth before a fall' and is the time one needs to be wary. I am trying to be more alert, sometimes it seems to be very slow progress, but still it is progress I am sure. If you have any advice to offer as to how to learn to think, how to get something of an education when old, &c., it will be gratefully received."

Her greatest difficulty was in household administration and she did not discipline the younger children as she had done when she herself was younger, although her general health was excellent. Nevertheless, she was still careful of her own person and orderly. Her sense of humour, memory, and insight into the thought and feelings of others was altogether unimpaired. She was capable of intelligent conversation and did not talk either more or less than good taste demanded. Another letter from California may be quoted, written this time on the first aniversary of her operation:—

> "It has been a very wonderful year with new life, new strength, new hope . . . I need firmly to convince myself that I am not really slow, nor stupid, not incapable, &c., and the rest will come.
>
> "We will often think of you at Christmas and I am thankful I can picture you as you will be—the sunshine in the dining room and study, the cheery open fire, and the children going out to skate and coast or ski, the cars slipping and sliding, the cold crunch of the snow."

This shows insight, vivid memory and power of expression. In her home there was little or no discord. Her husband was patient and sympathetic and her children reflected the unselfish personality of their mother. Her own home provided in some ways a better background for study than the consulting room of the psychologist. The following test, though not sanctioned by psychological usage, may illustrate her shortcomings.

One day about fifteen months after operation she had planned to get a simple supper for one guest (W. P.) and four members of her own family. She looked forward to it with pleasure and had the whole day for preparation. This was a thing she could have done with ease ten years before. When the appointed hour arrived she was in the kitchen, the food was all there, one or two things were on the stove, but the salad was not ready, the meat had not been started and she was distressed and confused by her long continued effort alone. It seemed evident that she would never be able to get everything ready at once. With help the task of preparation was quickly completed and the occasion went off successfully with the patient talking and laughing in an altogether normal way.

Although physical examination was negative and there was no change in personality or capacity for insight, nevertheless the loss of the right frontal lobe had resulted in an important defect. The defect produced was a lack of capacity for planned administration. Perhaps the element which made such administration almost impossible was the loss of power of initiative. If we express it as she did with no attempt at analysis: she could not "think well enough," was a little "slow," a little "incapable."

In Case 3 the removal of the frontal pole, about half of the lobe, produced no detectable loss of function. This may be due to the fact that we could not study this boy before his accident. Or it may be due to the fact that the anterior one half of the frontal lobe subserves only transferable function.

CONCLUSIONS.

Large amputations of the frontal lobe, if the precentral gyrus be left intact, produce surprisingly little disturbance of function which can be detected by ordinary methods of examination. There is no disturbance of the control of micturition, no forced grasping, no alteration of tone of the extremities or in the activity of deep or superficial reflexes.

In Case 2 the operative removal affected only the middle one-third of the left frontal lobe, as the anterior one-third had already been destroyed by the traumatic injury, if one may arbitrarily so divide the lobe. This removal of the middle one-third in a right-handed man produced a partial loss of his capacity for mental arithmetic (oral as distinguished from written). The patient also had an unexplained absence of dizziness and past-pointing after rotation and caloric tests, even though vestibular function was otherwise normal.

Detailed studies of sensation showed only changes that we presume to be within the limits of normal spontaneous variation. In Case 2 there was decreased appreciation of figures written upon the palm of the contralateral hand which may perhaps be related to the difficulty that the patient noted in the visualization of figures in "mental arithmetic."

The removal of approximately the anterior half or two-fifths of the right frontal lobe in Case 3 was not associated with any alteration, neurological or psychological, that we can detect.

The two larger removals (Cases 1 and 2), present certain important defects in common and we consider these removals to have begun at the time of the origin of the initial lesion and merely to have become complete at the time of operation. Neurologically each was normal. By the ordinary psychometric tests each would have to be judged normal although neither would rank very high. Each patient was lacking in initiative. Each was very good-natured and co-operative which may in some cases perhaps be an evidence of lack of initiation of ideas. Although it may not be of value here we may also remark in passing that we have in several other cases been told by relatives that removals of a very large area of frontal lobe with included neoplasm have resulted in marked improvement in the patient's temper.

Insight and capacity for introspection were preserved. Capacity to follow instruction was unimpaired, but initiative and capacity for planned action were clearly defective. This was especially true of the woman of 43. She had become incapable of discerning for herself possible courses of action so that she might choose. If others presented to her the possibilities she made up her mind quite easily, and when a task lay before her there was no reluctance nor hesitation in undertaking it.

In so far as final conclusions from the first two cases are justifiable, it may be stated that maximum amputation of right or left frontal lobe has for its most important detectable sequel impairment of those mental processes which are prerequisite to planned initiative.

NOTICES OF RECENT PUBLICATIONS.

Intercortical Systems of the Human Cerebrum. By JOSHUA ROSETT. Milford: Columbia University Press, 1933. Pp. 135, with 41 illustrations. Price 15s.

The ingenious method of splitting the white matter of the brain into its natural layers devised by the author has been applied by him with painstaking skill to the study of the intercortical pathways of the human cerebrum. Briefly the method consists in "exploding" the brain by saturating it with CO_2 under pressure and suddenly releasing the pressure. The layers of cleavage are then carefully dissected out and studied in flat sections stained by the Weigert-Pal method. The value of this method for the study of the intercortical connections is well shown by the present monograph, although the author confesses that the cartography of these systems is by no means complete. But even in the short time that has elapsed since the method was perfected the main subcortical and deeper connections have been mapped out. Among the many interesting observations which the book brings to light, the shortness of the subsulcine U fibres, and the fact that they are interrupted by any annectant gyrus in their path is somewhat surprising. The author has also shown that the inferior longitudinal fasciculus consists of many shorter systems uniting neighbouring parts of the brain, and that few if any fibres pass in it from the occipital to the frontal pole.

In addition to providing a remarkably complete survey of the white fibres of the cerebrum, the author has been able to criticize the work of the older investigators in the light of the new facts which his technique has furnished. The monograph is thus not only a record of original observations, but a well-informed survey of the whole field of intercortical fibres systems.

L'Angiographie cérébrale. Par EGAS MONIZ. Paris: Masson et Cie, 1934. Pp. 327. Price 90 fr.

In this monograph Professor Moniz has given an account of his experiences with "thorotrast" since the autumn of 1931. This substance has been found to possess many advantages over sodium iodide which was used in his earlier work. It appears to be non-toxic and safe. But it is specially valuable because, as it mixes slowly with the blood, it can be followed into the intracerebral veins and venous sinuses. This property also enables it to be used for injections of the vertebral artery, via the common carotid. It is thus possible to investigate every region of the brain for the presence of a tumour or aneurysm. By taking a series of plates at intervals of two or four seconds the rate of the blood-flow through any arterial system can be timed, and the presence of arterial stenosis or aneurysm may thus be diagnosed. The method has also been used in the diagnosis of congenital malformations in the Circle of Willis.

The technique of the injection is comparatively simple, but the interpretation of the plates would be difficult without an accurate knowledge of the normal appearances of the cerebral arteries and veins when viewed by this technique. A large part of the book is, therefore, taken up with a description of the normal and with the more common abnormalities. This description is greatly aided by the series of excellent plates. Altogether it is a valuable guide to a method of diagnosis which is now emerging from the experimental stage and being widely used.

Une Nouvelle Syphilis Nerveuse, ses formes cliniquement inapparentes. Par PAUL RAVAUT. Paris: Masson et Cie, 1934. Pp. 200. Price 45 fr.

In this monograph Ravaut sums up his experiences, over a period of more than thirty years, of the cerebrospinal fluid during the secondary and latent periods of syphilis. The evidence which he collects is impressive although not altogether concordant. On the whole he makes out a strong case for the assumption that clinical neurosyphilis is based in the vast majority of cases on an infection of the meninges of the nervous parenchyma during the late primary or secondary periods of the disease. The frequency of such infection, as shown by the statistics of many workers, varies from 51 to 86 per cent. in acquired, and from 25 to 100 per cent. in hereditary cases. The percentage of meningeal reactions appears to be greatest between six months and two years after infection, dropping rapidly towards the close of the third year. Which of these cases are destined to be included in the 15 per cent. of clinical neurosyphilis is a question which Ravaut has set himself to settle. The answer he gives is that those cases with "complete" reactions (i.e. not only excess of cells and protein, but also positive Wassermann and colloidal reactions) in which the fluid returns slowly and incompletely towards normality under treatment will probably develop neurosyphilis later. A similar prognosis may be made apart from the results of treatment when the cell count includes plasma cells and polymorphonuclears as well as lymphocytes. But it appears to be impossible to foresee what form the clinical disease will take. He is convinced that the solution of the problem of neurosyphilis lies in thorough treatment during the primary and secondary stages of the disease controlled by lumbar puncture, which should be performed at least at the end of the third year. The value of malaria in the prophylaxis of neurosyphilis which has been suggested by recent Viennese work is discussed towards the end of the book.

As a survey of the author's life-work this book is of value, although, in spite of its title, it contains little that has not already been published. It suffers from the lack of a comprehensive bibliography and of an index.

Speech Disorders: A Psychological Study of the Various Defects of Speech. By S. M. Stinchfield. London: Kegan Paul. 1933. Pp. 341. Price 15s.

The merit of the first part of this book, dealing with the nature of speech disorders, lies in the setting forth of divisions and of relevant bibliography rather than in its mode of presentation which is neither as critical nor as well-informed as one would wish. Evidently with enormous labour the writer has read all she could find concerning her subject, but where clinical experience and selection were necessary she has fallen short. The lengthy chapters on: "Pathological Conditions Affecting the Speech Function—Dysarthria Cerebropathica, Dysarthria Neuromusculopathica"; on "Dysphemia, or Backgrounds which Produce the Stutterer—Dysphonia or Voice Defects" and on "Dyslogia and Dysphasia" are bookish and artificial on this account. If one may judge from the lists of Greek neologising given in Part I, there is now among the psychologists who study this subject a rage for classifying and naming which is reminiscent of the older days of psychiatry. The second part of the book gives the statistical findings in some personal investigations. These were made by Dr. Stinchfield on 3,000 college women and some public school groups, and they covered personality, left or right-handedness and oral and silent readings in their relation to speech. Questionnaires and tests were used. The book is detailed but contains much undigested factual material.

Die Neurologie des 1—7 Jahrhunderts n. Christus. By Dr. Walter Creutz. Leipzig: Georg Thieme. 1934. Pp. 106. Price M. 7.80.

As Dr. Creutz points out in his foreword, neurology has received little attention from the historians of medicine. This gap he has essayed to fill for the period that stretches roughly from the Augustan Age to the fall of the Empire of the west. Beginning with Celsus, he takes in turn Soranus and Coelius Aurelianus, Aretaeus, Oribasius, Aetios, Alexander of Tralleis and Paulus Aegineta, and translates into German the relevant passages in their writings. Galen he mentions only briefly here as Falk's comprehensive monograph is available, but in the suceeding section, in which he makes a comparative study of the knowledge and theories of the period, he devotes much space to this incomparable observer. The zenith of neurological study during the Roman Empire was in the first two or three centuries when there flourished not only Galen but the clinicians with Soranus at their head, and Aretaeus only a short distance after him. This carefully written monograph is a valuable source-book for the many data of neurological interest which are scattered rather inaccessibly through the extant writings of an interesting, if remote, age of medicine.

Lateral Dominance and Visual Fusion. By C. A. SELZER. Harvard Monographs in Education. No. 12. Cambridge: Harvard University Press. 1933. Pp. 119. Price 6s.

This monograph deals with the relation of heterophoria and alternating vision to the disabilities in reading, writing, spelling and speech generally, which are such a handicap educationally to some children. The alleged importance of lateral dominance, especially as seen in hand and eye, is examined, and the author puts forward with indignant zeal his conviction that treatment of mirror-reading and related troubles should be by the wearing of prisms; oculists are on the whole understandably dubious about his claims. The discussion of tests for lateral dominance is an interesting part of the monograph.

L'Enfant et le Langage. Par HENRI DELACROIX. Paris: Librairie Félix Alcan. 1934. Pp. 118. Price 12 fr.

M. Delacroix here carries further some of the questions raised in his well-known larger work on language and thought. Many studies on the development of speech in children have appeared in the last few years, and here they are examined critically. The superficial formulations which sometimes pass muster in psychology are exposed, and the valuable findings of Stern, Yerkes, Kellogg, Bühler and others are reviewed. Although brief the book leaves few aspects of the subject untouched, and the style is, as always with the author, felicitous.

Konstitution und Prozess in der Schizophrenie. von Dr. Skalweit. Leipzig: G. Thieme. 1934. Price M. 4.50.

The author has applied the Rorschach method to the study of schizophrenia, especially "Prozess-Schizophrenie." The problem which particularly occupied his attention is not, however, so prominent in English psychiatry, where the conception of a schizophrenia determined by progressive structural changes has not had general recognition.

From the results of his investigation he concludes that a schizophrenic psychosis does not consist in a purely quantitative intensification of the specific schizoid type of reaction but in a qualitative change in this. He draws unduly wide inferences from a test that is still on probation. The typological doctrines of Kretschmer are also examined, and the author shows his interest in some national pre-occupations by a discussion of the relationship between the schizothyme type and the Nordic race.

Investigation into the Causes of Mental Deficiency. By H. O. Wildenskov. Copenhagen: Levin and Muskgaard. London: Humphrey Milford. 1934. Pp. 113.

The author of this work, who is the medical superintendent of a Danish institution for mental defectives, has carried out a careful and painstaking research into the differences in family incidence of deficiency between two groups of his patients, the one group being composed of fifty mild cases and the other of fifty severe ones. Various additional aspects of the two groups were also investigated, but the family studies supplied the most important data on ætiology. With a refreshing lack of mathematical ostentation Dr. Wildenskov presents his material and points out how much fewer were the definitely exogenous cases that is often asserted to be the common proportion. He emphasizes that the discovery of neurological abnormalities does not necessarily indicate pre-natal or post-natal trauma, since inheritable structural anomalies or predispositions may be in question. In view of the relatively small numbers he is cautious in his conclusions, but he finds strong evidence of the hereditary factor being more significant in the mild than in the severe cases.

Mental Health: Past, Present and Future. By A. H. Ruggles. Baltimore: The Williams and Wilkins Company. 1934. Pp. 104.

These attractively composed lectures have a welcome honesty and lucidity. There are three of them: The first is historical, while the second deals with the present situation in psychiatry, especially in its American developments. The last lecture, which looks to the future, is soberly optimistic about mental health. The author puts his hope in better training of physicians and other leaders, as well as in better training of the public, who must not only be led but co-operate, so that the social and individual problems which weigh so heavily now may be lightened if not solved.

Die Irrtümer der Psycho-analyse. By Henrik Egyedi. Vienna and Leipzig: Wilhelm Braumüller. 1933. Pp. 86. Price Rm. 2.80.

While the majority of observers are now content to show distrustful politeness, or at least reserve, towards psycho-analysis, there are some who are goaded into critical or irritable examination of its claims. These provocative claims are more or less proof against such onslaughts, because it is not to the court of logic or scientific method that psycho-analysis appeals. The objections made here by Dr. Egyedi are in the main valid if applied to any scientific procedure where the necessity for repeating and verifying observations, testing hypotheses, and predicting outcomes in given circumstances can be taken for granted. But psycho-analysis is not a procedure of this kind;

statistical and other controls have played practically no part in it. Some of his strictures are less applicable to the strict doctrine of Freud himself than to the still more speculative form that has developed in this country in the last few years. On the other hand, it is no longer possible to accuse the Freudians, as the author does, of a slavish devotion to their master; the devotion of psycho-analysts is now becoming, like so much else, national or local, and London looks backwards and sideways, not upwards, upon Vienna. It is doubtful, whether, such methodological examination as this will have much more effect than had the similar criticisms of phrenology or homœopathy. Psycho-analysts are by temperament and training unlikely to be influenced by attacks on such lines, even when mitigated by admiration for Freud; others will prefer to wait until the hypotheses of psycho-analysis can be satisfactorily tested.

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EDITOR.

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LESIONS OF THE CENTRAL AND PERIPHERAL NERVOUS SYSTEMS PRODUCED IN YOUNG RABBITS BY VITAMIN A DEFICIENCY AND A HIGH CEREAL INTAKE.

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IN previous publications [1 (*a*), (*b*), (*c*), (*d*), (*e*), (*f*)] accounts have been given of the dietetic methods whereby degenerative changes in the central and peripheral nervous systems of young dogs and rabbits can be produced and prevented. The two outstanding factors which, when associated together, produce these changes are: (1) A deficiency of vitamin A and carotene in the diet; and (2) a high cereal intake. Of these, the absence of vitamin A and carotene is probably the more important in young animals, for if either is added to the basal diets so far tested the degenerative changes do not occur. On the other hand, when vitamin A and carotene are deficient, the nerve degeneration can be made worse by altering the amount and type of cereal eaten, or in the dog by adding certain cereal products such as the embryo on ergot.

Except for one publication [1 (*e*)] in which the effects of vitamin A and carotene deficiency in producing xerophthalmia in rabbits were related to degenerative changes in the ophthalmic division of the trigeminal nerve, most of the published results referred to experimental work on dogs. It seemed desirable, therefore, that a fuller account should be given of the complex changes in nerve-cells and nerve-fibres which can be readily produced in young rabbits by similar dietetic means. Clearly, for a herbivorous animal like the rabbit, the basal diet must be of a different nature from that used in the dog experiments, and yet the same specific dietetic defects must be present in both.

Experiments were originally begun on rabbits with the object of discovering if possible the chemical nature of the substances in ergot and in cereals which act as neurotoxins in dogs and probably in man in the absence of vitamin A and carotene. It was hoped that it would be easier to continue this part of the work on smaller and cheaper animals. Thus, it happened that the diet of many experimental rabbits in this series contained either ergot, or some extract or residue of this substance. As the work progressed, however, it became more and more questionable whether ergot affected the nervous system of rabbits even in the absence of the protective substances. In any case its neurotoxic action did not seem as potent in the rabbit as in the dog under the experimental conditions so far tested. It is certain that most, if not all, of the specific nervous lesions to be described can be readily produced in rabbits by withholding carotene and vitamin A and without giving ergot or ergot derivatives.

Although the present investigation has been fairly extensive and includes the examination of central and peripheral nerves as well as many groups of cells and ganglia in a large number of rabbits it is by no means complete. A neurological expert would undoubtedly find many other points of interest both in the behaviour of the animals and in the lesions of the nervous system produced by these specific nutritional conditions. This work, however, may lead others to extend the inquiry.

EXPERIMENTAL CONDITIONS.

Litters of rabbits of eight to ten weeks old were used. The basal diets had to be such that they were compatible with good health and growth during the period in which the specific lesions developed. The following diet deficient in carotene and vitamin A was found to fulfil this object.

The main ingredients were 4 parts of oats and 1 part of bran to which calcium carbonate was added to form 1·5 per cent. of the mixture; lemon-juice was given in some of the experiments as a source of vitamin C. According to the age of the rabbit, 40 up to 70 grm. of the oats-bran mixture, together with a constant amount of 10 grm. of dried alfalfa which had been heated at 120° C. for thirty-six hours, were given daily. The alfalfa was ground to a fine powder and then heated in thin layers on trays in an electric oven and stirred frequently during the heating process in order to allow full exposure to the air. By this means its carotene content could be entirely destroyed. A point of importance for the production of severe lesions is the degree of destruction of the carotene in the alfalfa. If it be only partially destroyed, there may be little or no degeneration, or it may develop slowly and not be severe. For intense lesions to develop rapidly the heating and stirring of the alfalfa must be sufficient to ensure the complete destruction of the carotene. If unheated instead of heated alfalfa be given, the nervous lesions do not appear. Similarly, if cabbage or carrots or any other source of carotene or vitamin A be added to the standard basal diet, the nervous system of the rabbit is protected. Pure carotene, in amounts of 1 to 3 mgm. daily, was sometimes added to the basal diet to prevent the nerve changes. In view of Stockman's results [2] in which he has produced derangement of the nervous system by diets rich in cereals but containing very little available calcium, it is necessary to point out that in the present work there is no deficiency of available calcium in the diet. It may also be well to add that in each series of experiments a rabbit with a normal nervous system has been produced by adding a source of the protective factor to the same basal diet as that given to the affected animal.

Behaviour of rabbits on the carotene-deficient diets.—The young rabbits grow and remain well on the basal diet for some months. The order of the appearance of signs of nerve defect varies, but slight stiffness of the legs, and especially of the hind legs, is generally the first abnormality noticed; this may be seen after two to three months of the experimental diets. Xerophthalmia appears next, three to six months after the beginning of the experiment; a dull patch or band appears on the cornea, usually in the centre, running midway between and parallel to the eyelids, i.e. in that part most exposed [1 (*e*)]. At this stage examination will show that the pupillary reactions are sluggish. Head movements usually develop quickly after this, although in some cases they are noticed before the changes in the eyes. The animal moves its head in a curious and characteristic way, as if it did not know its position in relation to the rest of the body; sometimes it is moved up and down and sometimes from side to side, and when at rest is often askew with ears awry. In the later stages of xerophthalmia some of the head movements may be due to ocular defects and obscured vision. The rabbit often moves about as if suffering from alcoholic intoxication. It may go round in circles, turn its head permanently towards one side, wobble from side to side, and in extreme cases even fall over either to the side or backwards, sometimes being unable to regain the normal position.

When examined in the cage the early signs are not so obvious; the animal has a sleepy look, the eyes often being half closed; it sits quietly huddled in the corner of its cage.

At no time is there any definite paralysis, but the animals appear heavy on their legs and show less spontaneous movement both in the cage and outside, and in advanced cases often refuse to move at all.

It will be seen below that the lesions of the central and peripheral nervous systems are often very extensive, and no doubt a closer examination, especially tests on the sensory side, would reveal many other functional defects. A casual examination, however, makes it clear that the co-ordinating mechanism both of the head and body generally is defective, and in some cases it is obvious that the animals are blind and probably deaf.

Histological methods for demonstrating changes in nerve fibres.—Post mortem changes due to a lapse of time between death of the animal and fixation of its tissues were avoided. In some cases it was found better to fix the tissues *in situ*, but large organs and those with resistant capsules were dissected out and the tissues placed in the fixative.

A series of experiments on peripheral nerves was undertaken in order to compare the appearances produced by rough handling in post mortem dissection and those found in experimental animals. Nerves which were crushed with forceps, stretched or left for periods up to forty-eight hours after death of the animal gave positive Marchi reactions, but in these cases the appearances were not the same as those produced by lack of carotene or vitamin A. Needless to say, changes produced by trauma were avoided as much as possible.

The tissues were usually fixed in formalin (10 per cent. tap water neutralized formol saline).

Although methods have been used for observing changes in the axis cylinders, those for demonstrating degeneration of the myelin in the fatty sheaths have received most attention. These include: (1) Osmic staining by Marchi's method (with modifications); (2) Nile blue and sulphurous acid (Lorrain Smith [3]); (3) Scharlach R.

For peripheral nerves, on the advice of Sir Charles Sherrington, a method described by Ramon-y-Cajal [4] was also tested in the later experiments. Fresh nerves were stained for ten to sixteen hours in 0·5 per cent. osmic acid, washed in distilled water, treated with alcohol and glycerin, and then teased before microscopic examination. This method is only useful in the case of peripheral nerves, in which it shows up the changes very beautifully (Plate VI, figs. 5 and 6).

For the staining of axis cylinders several silver methods were tried, but sufficient experience of this technique was not obtained to warrant description of the results, especially of the earlier stages of axis cylinder degeneration, in the present publication. Changes certainly are seen in the axis cylinders of the nerves of rabbits fed on carotene-deficient diets before advanced myelin degeneration occurs.

In order to determine the position of complete disappearance of groups of nerve fibres, Kulchitsky's modification of the Weigert-Pal method was adopted.

OBSERVATIONS ON THE HISTOLOGICAL RESULTS OBTAINED BY THE ABOVE METHODS.

When examining nerve fibres most attention was fixed on the myelin sheath and the changes it was liable to suffer under the prescribed experimental conditions. It is well known that histological methods for demonstrating demyelination changes, especially those involving the use of osmic acid, are apt to give unreliable results unless examined very critically. A great effort was made to avoid wrong interpretations of the experiments owing to misleading pictures; most of the animal experiments were repeated many times: the tissues from each animal were in many cases stained by several methods, and, when adopting any given technique for unknown tissues, sections of material known to be normal were often carried through simultaneously.

When the animals are severely affected there is no difficulty in demonstrating degenerative changes in the nervous tissues; when, however, the effects are slight it is by no means easy with the methods at present available. In early cases only two or three scattered fibres in a tract may be grossly changed; sometimes, for instance in the posterior roots, none show typical Wallerian degeneration, that found being rather of the annular type (see Plate VI, fig. 3). In this form the fibres are swollen, the myelin is altered in chemical composition but is not yet disintegrated, so that in cross section stained by Marchi's technique axis cylinders are seen surrounded by a dark ring of altered myelin stained with osmic acid. This annular type of degeneration is commonly found in the peripheral nerves of rabbits fed on carotene-deficient diets, but more rarely in the central nervous system. There is evidence that nerves so affected can be brought back to normal fairly rapidly when the deficient nutritive agent, in this case vitamin A or carotene, is supplied to the animal. This point, which I have discussed elsewhere [1 (*e*) (*f*)] in relation especially to degenerative changes in the ophthalmic division of the fifth nerve in cases of xerophthalmia, is one demanding much closer study both because of its scientific and its practical interest. When the degeneration is more advanced and the myelin sheath has disintegrated, structural recovery takes a much longer time.

The probable interpretation of the differences between the changes seen in the nerves of the carotene-deficient animals and those which are more familiar, namely, so-called Wallerian degeneration following injury when the axon is actually or virtually separated from its cell of origin, is that in the former the changes come on more gradually and are much more prolonged. The structural changes following nerve section are well known and the appearance of a fibre at different times after severance from its cell of origin can be more or less accurately foretold. For instance, fourteen to sixteen hours after section, Marchi's staining method will usually show the myelin sheath of the distal part of the nerve to be intact although stained with osmic acid; this, presumably the annular stage, is rapidly passed, however, and in the course of another eight hours the myelin sheath is breaking down and droplets are seen invading the axis cylinder. It seems probable, therefore, that the changes following injury and those caused by altered metabolism (toxic) differ only in degree and not in kind.

Toxic degenerative changes are much less understood, and, as regards the particular problems under discussion in this paper, have not previously been the subject of study. As might be expected from allied work on other animals, the time of onset and the degree of severity of the nerve lesions in rabbits fed on carotene-deficient diets varies. The age of the animal at the beginning of the experiment, the prenatal and postnatal feeding and probably the rate of growth and breed, all affect the results. The reason for these influences can in some cases be understood. For instance, it is obvious that a rabbit with large stores of vitamin A in the liver at the time of the initiation of the experimental feeding will resist longer the influence of a carotene-deficient diet than one with only small stores of this substance. Similarly, a rapidly-growing animal might be expected to use up its stores more quickly. But some of the factors influencing the rate and severity of the onset, especially the question of age, are more difficult to understand. Age seems to bring about a greatly increased stability of the nervous system, and an adult animal is very resistant to the dietetic influences discussed here which in younger animals rapidly result in extensive degenerative changes in parts of the nervous system.

In some experiments in the series the animals were killed soon after the general signs of abnormality were first observed; in others a longer interval was allowed so that degeneration was more extensive. Sometimes, after the morbid condition had been produced, a source of carotene or vitamin A was added to the diet, with the result that further degeneration was prevented and curative changes were observed. This part of the problem will be discussed in a later paper.

Distribution of nerve degeneration in carotene deficient rabbits.—An account will now be given of the more common positions of the different levels of the brain and cord in which lesions are found in rabbits brought up on diets previously described where vitamin A and carotene are deficient. As it is not easy to take low-power photomicrographs of Marchi preparations which show up the degenerated fibres, it was decided to make drawings showing the position and relative amount of degeneration at representative levels. At first it was thought that this would give as accurate a record as the work justified. On further consideration, since it seemed certain that some at least of the fibres involved in more obvious lesions could be identified, as those of the dorsal columns and of the spino-cerebellar tracts, attempts were made to associate more and more of the degenerated fibres with well recognized tracts. This procedure became more necessary when the medulla, pons and mid-brain were examined, as it was desirable if possible to make some kind of a unified story out of what at first sight seemed a mass of disconnected facts. The distribution of the degenerated fibres in the medulla and pons has helped considerably in the identification of degenerated fibres in the cord, for many tracts which are in close proximity in the latter separate out in the higher regions and therefore can be more readily differentiated. I have therefore attempted to describe the actual degenerative changes in terms of well-recognized tracts, in spite of the fact that in so doing some errors may have been made.

Although the brain-stem of the rabbit is built up on the same plan as that of other mammals, variations in the size and position of some of its component parts are apt to lead to difficulty in recognizing certain groups of nerve fibres and nerve cells (nuclei). For instance, the inferior olivary proturbances in the rabbit are small as compared with those of man. Again, in the human brain a large band of transverse pontine fibres are seen superficially, while in the rabbit the pons is a relatively small structure (see fig. 1) so that these fibres form a comparatively narrow band. Before attempting to identify the lesions in the affected animals, it was thought desirable to fix the "land marks" of the brain of the rabbit as compared with other mammals and for this purpose serial sections (30μ thick) were made right through the brain of a normal animal. Every tenth section was stained with hæmotoxylin after mordanting, so that a general view of the main anatomical and histological arrangements in the rabbit's brain was obtained (fig. 1) and compared with similar levels in man and dog.

Even when the general relationship of the larger features of the brain are grasped, differences in the relative number and position of fibres forming established tracts in different species also bring difficulties in describing lesions in detail. The rabbit, in common with many other mammals, has no direct pyramidal tract in the ventral column so that the intense degeneration in this column, and especially in the fibres adjacent to the ventral fissure so commonly seen in the affected rabbits in this work, cannot belong to the direct pyramidal tract. Corroboration of this deduction is obtained by the fact that even in fairly severely affected animals it is rare to find degenerated fibres in the pyramidal tract of the pons and medulla, or in the crossed pyramidal tract of the cord.

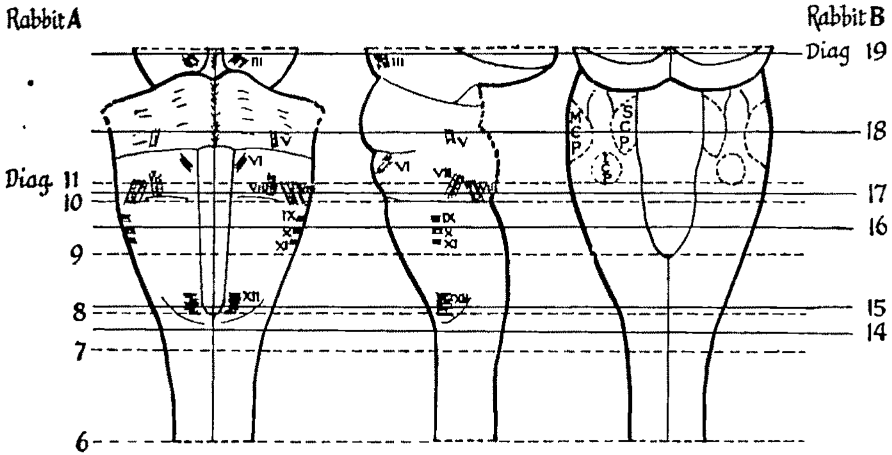

FIG. 1.—Diagrams of dorsal, lateral and ventral aspects of a rabbit's brain-stem to show the relative positions of diagrams 6-11 (rabbit A) and 14-19 (rabbit B).

A still further difficulty in interpreting lesions of the brain-stem is that, although the main tracts in the central nervous system of man and some animals have long been established, there are still many groups of neurons of whose origin, distribution and termination little is known, and this seems to be especially true in the case of some common laboratory animals like the rabbit and rat.

In face of these difficulties it may be necessary to amend the names given here to some of the degenerating tracts; the positions indicated in the figs. 3 to 19, however, represent the lesions as found in the majority of the experimental animals fed on carotene-deficient diets.

In view of the varied nomenclature adopted by different workers to distinguish any one tract, it may be well to add that in this publication: (1) The terms lumbar, thoracic and cervical have been used for the three main regions of the cord; (2) that in cross-sections of the cord the three main divisions into which the long fibres are broken by the gray matter are referred to as the dorsal, lateral and ventral columns; (3) as far as possible the names used for the tracts indicate the origin and destination of the fibres. When two groups of fibres are found in different positions and yet have the same endpoint and the same origin they are referred to as ventral, dorsal or lateral in relation to each other, e.g. ventral spino-cerebellar and dorsal spino-cerebellar (both in lateral columns), also ventral spino-reticulo-thalamic (ventral column) and lateral spino-reticulo-thalamic (lateral column) (see fig. 2).

RABBIT A.

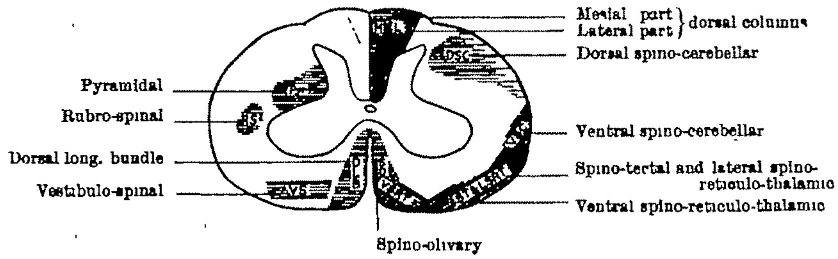
Mesial part } dorsal columns
Lateral part } dorsal columns
Dorsal spino-cerebellar
Pyramidal
Rubro-spinal
Ventral spino-cerebellar
Dorsal long. bundle
Spino-tectal and lateral spino-reticulo-thalamic
Vestibulo-spinal
Ventral spino-reticulo-thalamic
Spino-olivary
DSC
RS
VS

FIG. 2.—Rough diagrammatic representation of the position of the main tracts in a rabbit's spinal cord.

The drawings seen in figs. 3 to 19 were made from representative sections (stained by a modified Marchi method) of the cord and brainstem of two rabbits (A and B) in which severe signs developed. Sometimes a section of one of these rabbits reveals the points it is desired to emphasize better than those of the other. The first animal A, shows much degeneration of the cerebellar tracts, whilst in the second animal B, most degeneration was found in the fillet. The diagrams do not represent the distribution of degenerated fibres in all the animals of this large series of experiments; they demonstrate, however, the positions in which degeneration is more commonly found.

Both rabbits had the same carotene-deficient diet (one had a daily addition of untreated and the other of treated ergot). In A the earliest symptoms appeared about the twelfth week and by the twenty-second week there was definite though slight inco-ordination. Xerophthalmia and head movements were seen about the twenty-third week, and by the twenty-fifth the animal was very inco-ordinate and had difficulty in regaining its balance when put on one side. It was killed on the twenty-eighth week, sixteen weeks after the first signs of nervous abnormality. The second animal B was on diet only eight weeks when it showed the first signs of abnormality, especially slight stiffness and head movements. These gradually increased although there was slight improvement over one period. After the twenty-first week its head was held permanently to the left and there was definite xerophthalmia. It was killed after twenty-five weeks (seventeen weeks after appearance of the first signs), when the inco-ordination was great and the head-jerks such that the animal tended to fall over backwards.

An examination of figs. 3 to 19 shows the distribution of degenerated fibres and tracts in the spinal cord and brain-stem. In these drawings, black dots represent degenerating fibres as revealed by Marchi method, circles "o" represent fibres which have completely degenerated, and not annular degeneration (see p. 145).

I.—SPINAL CORD.

Ascending tracts.—In the spinal cord degeneration is found in the following ascending paths:—

(1) In both tracts of the dorsal columns. It is more common to find degeneration in the lateral than in the mesial column.

(2) In the following tracts of the lateral columns:—

(*a*) dorsal spino-cerebellar;

(*b*) lateral spino-reticulo-thalamic;

[There is reason to believe that the ventral and lateral spino-thalamic tracts consist in part of fibres with synaptic interruptions, especially in the reticular formation of the brain-stem, and the two tracts are sometimes designated as the spino-reticulo-thalamic paths (Page May [5].]

(*c*) ventral spino-cerebellar; and

(*d*) in the spino-tectal;

[The fibres of this tract are in the cord associated with the lateral spino-reticular-thalamic tract, but it forms a separate tract in the mid-brain where degenerated fibres are seen (figs. 12 and 19).]

(3) In the ventral columns the most prominent ascending degenerated fibres belong to: (*a*) ventral spino-reticular thalamic (see note 2*b* above); and (*b*) possibly spino-olivary tracts.

Descending tracts.—There are degenerated fibres in the following descending tracts of the spinal cord: (*a*) the rubro-spinal; (*b*) vestibulo-spinal; (*c*) the dorsal longitudinal bundle. The extent of the dorsal longitudinal bundle in the rabbit is not definitely established.

The main descending tract, namely the crossed pyramidal, is usually quite free from degenerated fibres, although in some of the carotene-deficient rabbits a few degenerated fibres are occasionally found in what is apparently the crossed pyramidal tract.

It is interesting to note in connection with the obvious impairment of equilibrium in these rabbits that all the degenerated descending fibres so far identified are connected with the vestibular and cerebellar systems.

II.—BRAIN-STEM.

Ascending tracts.—In the brain-stem degeneration is found in the upward continuation of the ascending tracts of the spinal cord, including: (*a*) The dorsal spino-cerebellar, the degenerated fibres of which can be traced into the restiform body; (*b*) the ventral spino-cerebellar, fibres from which are seen entering the cerebellum via the superior peduncle; (*c*) the lateral and ventral spino-reticulo-thalamic tracts which pass close together through the brain-stem directly, or indirectly, to the thalamus; (*d*) spino-olivary; (*e*) degeneration is also found in the mesial fillet (composed largely of axons of cells in the nucleus gracilis and cuneatus); (*f*) in the lateral fillet which includes the second neurons of the auditory path; (*g*) the ascending fibres of the dorsal longitudinal bundle which connects the vestibular nuclei with the 3rd, 4th and 6th nuclei.

Descending tracts.—The descending tracts of the brain-stem showing degeneration include: (*a*) Rubro-spinal. Some degeneration is seen in the mid-brain where the fibres decussate (figs. 12 and 19) and in the medulla; in the pons and cord they are difficult to distinguish from degenerated fibres of other tracts; (*b*) vestibulo-spinal; (*c*) dorsal longitudinal bundle (below the vestibular nuclei).

Degenerated fibres are also seen in the intra-medullary portion of some of the sensory cranial nerves, especially the 8th and 5th.

It is interesting to compare and to contrast the behaviour during life with the amount of degeneration in the dorsal longitudinal bundles (vestibular connections) in these two animals: the head movements came on earlier and were much more pronounced in rabbit B than in rabbit A. Corresponding with this there was more degeneration in the dorsal longitudinal bundle of rabbit B. There was in rabbit A an access of degenerated fibres in the dorsal columns at the lowest medulla level (fig. 7) (compare with the dorsal column of Cervical II (fig. 6)).

In examining the individual drawings and comparing them with one another, it will be seen that the actual and relative number of degenerated fibres in many tracts vary in the different segments.

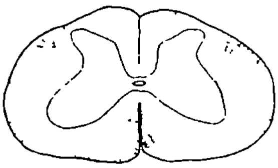

FIG. 3.—Lumbar, Segment IV.

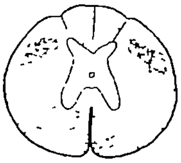

FIG. 4.—Thoracic, Segment VII.

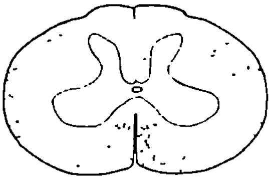

FIG. 5.—Cervical, Segment VI.

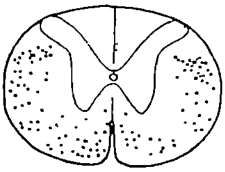

FIG. 6.—Cervical, Segment II.

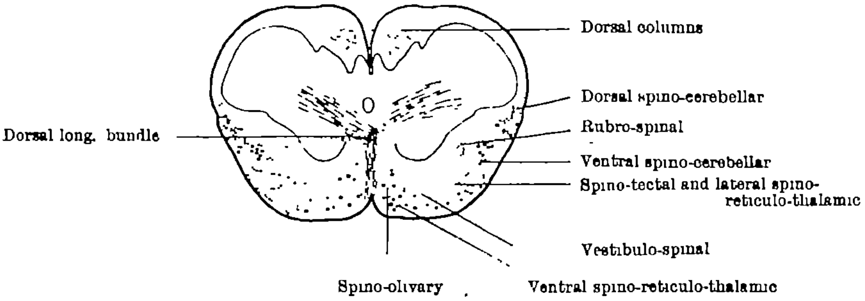

FIG. 7.—Medulla, pyramidal decussation.

Drawings illustrating degeneration in brain-stem and spinal cord of a rabbit on a carotene-deficient diet.

The following lesions were seen in the brain and cord of rabbits A and B.

Lumbar Segment IV (rabbit A) (fig. 3).—There are very few degenerated fibres in the dorsal columns; more are found in the cerebellar tracts and in the ventral columns adjacent to the ventral fissure. There is less degeneration in the lumbar and sacral regions than in any other levels examined. This is in general, true for all rabbits fed on these carotene-deficient diets.

Thoracic Segment VII (rabbit A) (fig. 4).—There are many more degenerated fibres in this level than in lumbar IV. Dogs brought up on diets deficient in vitamin A and carotene often had comparatively few degenerated fibres in the thoracic cord [1 (*c*)].

Cervical Segment VI (rabbit A) (fig. 5).—In this region the degeneration seems to have reached its maximum in the cerebellar and ventral column tracts, while the dorsal columns appear to contain fewer degenerated fibres than in the thoracic levels.

Cervical Segment II (rabbit A) (fig. 6).—The main change usually seen in this region is the scattered appearance of the degeneration in contrast to that in the lower levels of the cord; this is partly because the ascending tracts are separating out in preparation for redistribution in the brain-stem. At this level the degeneration in rabbit A is more evenly distributed between the lateral and mesial parts of the dorsal columns than is generally seen.

Medulla, pyramidal decussation (rabbit A) (fig. 7).—At the level of the motor decussation many degenerating fibres are seen in the dorsal columns near the nuclei cuneatus and gracilis, and also in the dorsal and ventral spino-cerebellar and lateral spino-reticulo-thalamic tracts. Rather less degeneration is seen in the white matter which includes the ventral spino-reticulo-thalamic, spino-tectal and spino-olivary tracts.

The fibres of the ventral columns naturally assume a more lateral position owing to the decussation of the pyramids, none of the fibres of which are affected, although some transversely cut fibres between the decussating ones are degenerated. These probably belong to the dorsal longitudinal bundle; there is some degeneration in what appear to be the vestibulo-spinal and the rubro-spinal tracts.

For the sake of clarity reference will first be made to some of the higher levels of rabbit A, then a few sections of rabbit B will be described.

Medulla, higher part of sensory decussation (rabbit A) (fig. 8). The inferior olivary and lateral reticular nuclei are just appearing at this level. Degenerated fibres are present in the remains of the dorsal columns, although many fibres have entered the nuclei gracilis and cuneatus. The axons of some of these cells can be seen sweeping through the reticular formation as internal arcuate fibres. There is much degeneration in the dorsal and ventral spino-cerebellar tracts but little in the mesial fillet (cf. fig. 15). The spino-reticulo-thalamic (above the level of the pyramidal decussation the lateral and ventral spino-reticulo-thalamic appear to run together), spino-tectal and possibly also the spino-olivary tracts contain some degenerated fibres and remain in approximately the same positions as in fig. 7. Of the descending fibres the dorsal longitudinal bundle and rubro-spinal tract show some degeneration; the vestibulo-spinal, still obscured by other tracts, is probably degenerated whilst the pyramidal is unaffected. The 12th nerve containing no degenerated fibres is seen passing ventralwards through the section.

Medulla, level of inferior olivary nucleus and the 4th ventricle (rabbit A) (fig. 9).—At this level in rabbit A there is not much degeneration in the fillet, but there is still heavy degeneration in the dorsal spino-cerebellar tract which is moving towards and entering the restiform body, the ventral spino-cerebellar, the spino-reticulo-thalamic and the spino-tectal tracts. There is some, but not much, degeneration in the dorsal longitudinal bundle; of the other descending tracts, the vestibulo-spinal and what appears to be the descending vestibular root of the 8th nerve contain more degenerated fibres. The latter has only been

RABBIT A.

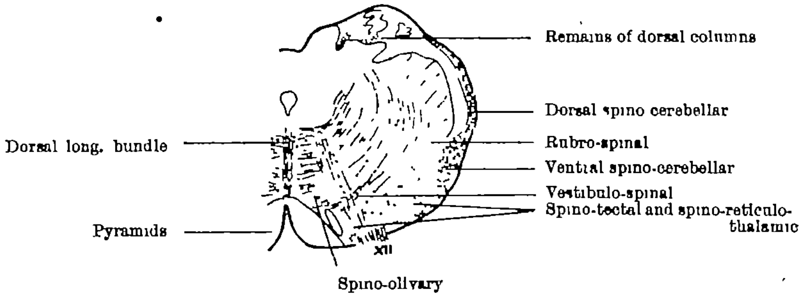

FIG. 8.—Medulla, higher part of sensory decussation.

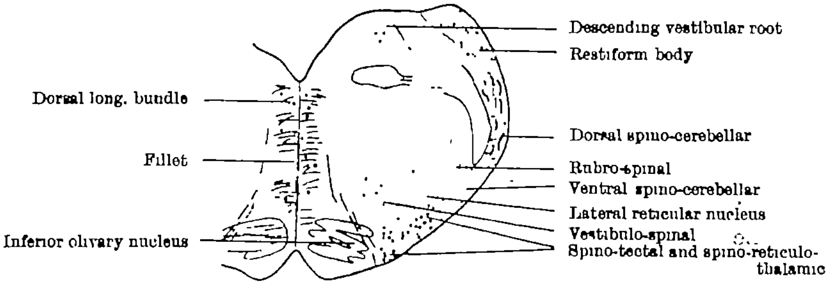

FIG. 9.—Medulla, level of inferior olivary nucleus and 4th ventricle.

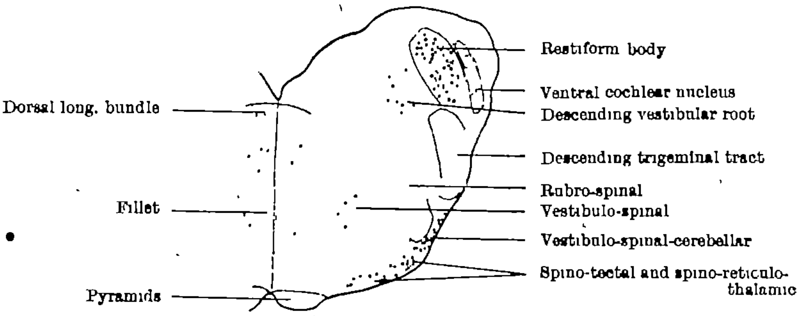
Restiform body
Ventral cochlear nucleus
Dorsal long. bundle
Descending vestibular root
Descending trigeminal tract
Rubro-spinal
Fillet
Vestibulo-spinal
Vestibulo-spinal-cerebellar
Spino-tectal and spino-reticulo-thalamic
Pyramids

FIG. 10.—Section between medulla and pons.

Drawings illustrating degeneration in brain-stem and spinal cord of a rabbit on a carotene-deficient diet.

traced as low as the higher levels of the nuclei gracilis and cuneatus. Some small degenerated fibres are present in the position of the rubro-spinal tract. It is interesting to note that in this animal there are degenerated fibres among the cells of the lateral reticular nucleus. These are only found in animals having much degeneration in the lateral cord columns and the restiform body. Rabbit B, which has less degeneration in the lateral tracts, does not show any degenerating fibres among these cells. The lateral reticular nucleus is said to relay impulses from the lateral tracts of the cord to the restiform body.

Section taken between medulla and pons (rabbit A) (fig. 10). The transverse pontine fibres are not seen although this section is taken above the level of the inferior olivary nuclei. A few fibres of the mesial fillet are affected. The large group of degenerated fibres on the latero-ventral aspect belong to the ventral spino-cerebellar, the spino-reticulo-thalamic and spino-tectal tracts. There is much degeneration in the restiform body, mainly dorsal spino-cerebellar fibres. Degeneration is seen in the dorsal longitudinal bundle, vestibulo-spinal tract, the descending vestibular root and also in a few fibres of the rubro-spinal tract. The pyramids are free from degeneration, as also is the descending branch of the 5th nerve. (In one or two experiments this branch of the 5th nerve contained degenerated fibres.) Degenerated fibres are also found among the cells of the ventral cochlear nucleus.

Level of the 8th and 7th nerves (rabbit A) (fig. 11).—In this section the transverse fibres of the trapezoid body can be seen. These, some of which are degenerated in rabbit A, arise in cells of the ventral cochlear nucleus and form the greater part of the lateral fillet of the opposite side (second neurons of the auditory path). The pyramidal tract contains no degenerated fibres and remains at the ventral surface of the brain-stem. The degenerating fibres of the ventral spino-cerebellar tract can be seen between the 7th and 8th nerves, bearing dorsalwards to enter the superior cerebellar peduncle. The restiform body has already entered the cerebellum in spite of the fact that the pons is not yet established. There is now much less degeneration in the ventro-lateral region since the ventral spino-cerebellar tract has moved dorsalwards and some of the spino-reticulo-thalamic fibres have probably entered relay stations in the reticular formation of the medulla. The only descending tracts in which degenerated fibres appear are the dorsal longitudinal bundle and the rubro-spinal. This section, being at the level of the 8th nerve, shows no descending vestibular root or vestibulo-spinal tract. Heavy degeneration is seen in the 8th nerve, while the 7th and 6th are unaffected.

Superior corpora quadrigemina (rabbit A) (fig. 12).—The only ascending tract containing degenerated fibres at this level is the spino-tectal. The others which showed degeneration in fig. 11 have probably entered relay stations; for instance, the spino-reticulo-thalamic fibres of the lower levels may have made synapses with cells in the reticular formation of the medulla and pons, some fibres of the lateral fillet have probably entered the nucleus of this fillet, and the ventral spino-cerebellar tract has entered the cerebellum via the superior cerebellar peduncle. Degeneration is, however, seen in the dorsal longitudinal bundle and in the rubro-spinal decussation. A few fibres of the 3rd nerve also take up Marchi stain. Although there is no degeneration in the internal capsule or the pyramidal tract of the lower brain stem, there are a few degenerated fibres in the crusta of this level.

Cervical, Segment II (rabbit B) (fig. 13).—It has previously been noted

RABBIT A.

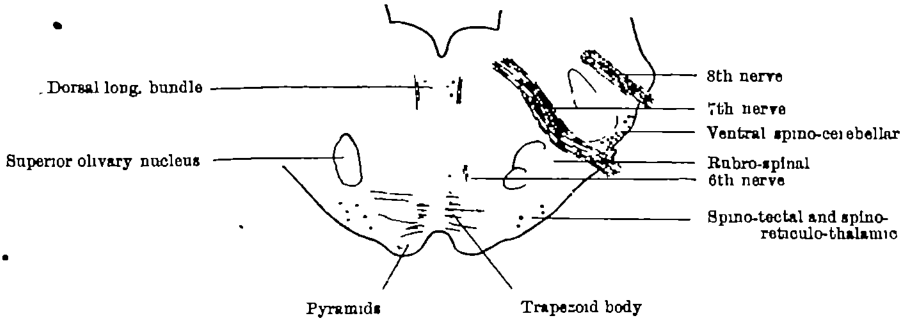

FIG. 11.—Level of 8th and 7th nerves.

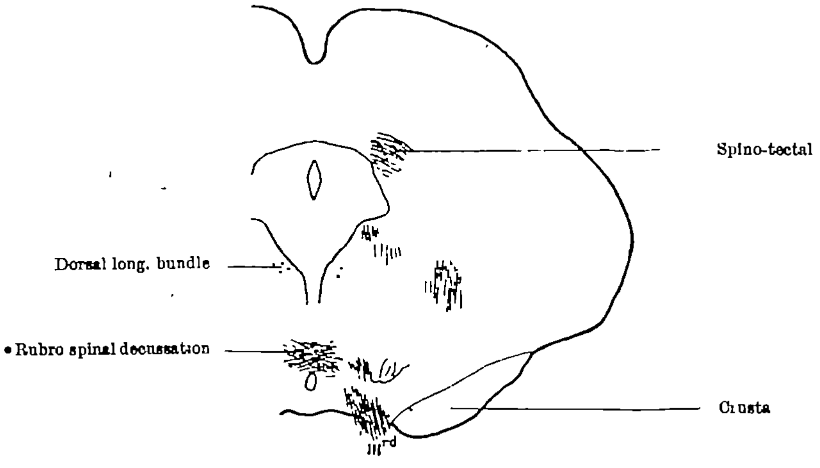

FIG. 12.—Superior corpora quadrigemina.

Drawings illustrating degeneration in brain-stem and spinal cord of a rabbit on a carotene-deficient diet.

that in rabbit B the degeneration is most prominent in the fillet and dorsal longitudinal bundle, whereas in rabbit A the heaviest degeneration is in the cerebellar tracts. This can be seen by comparing figs. 6 and 13. In rabbit B many fibres of the dorsal columns show very advanced degeneration with absorption of the myelin, and, as might be expected, there is also advanced degeneration of the second neurons of this path in the mesial fillet but no

RABBIT B.

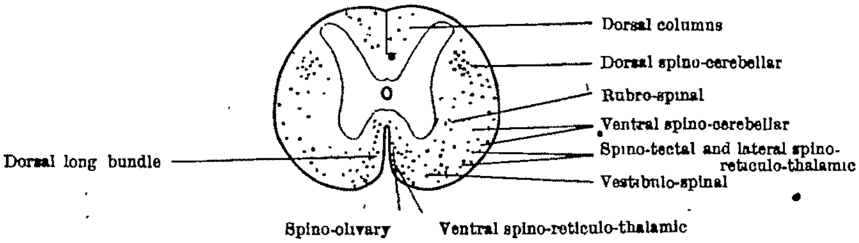

FIG. 13.—Cervical, Segment II.

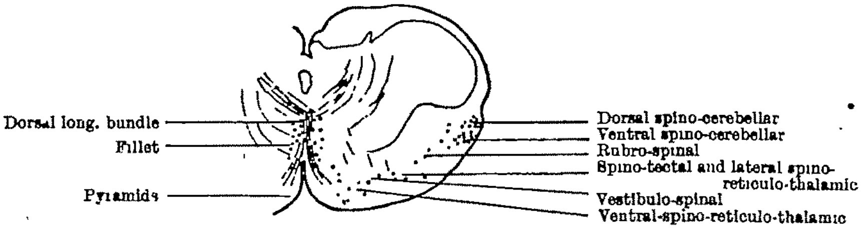

FIG. 14.—Medulla, lower part of sensory decussation.

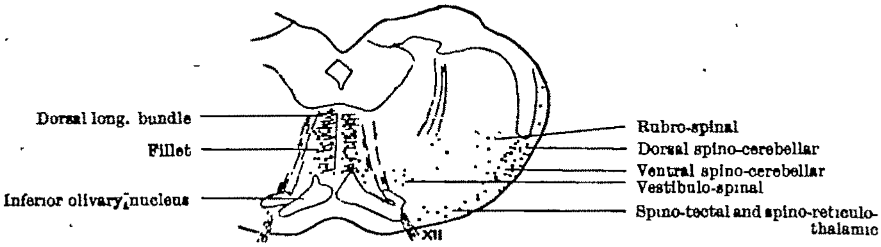

FIG. 15.—Medulla, level of inferior olivary nucleus.

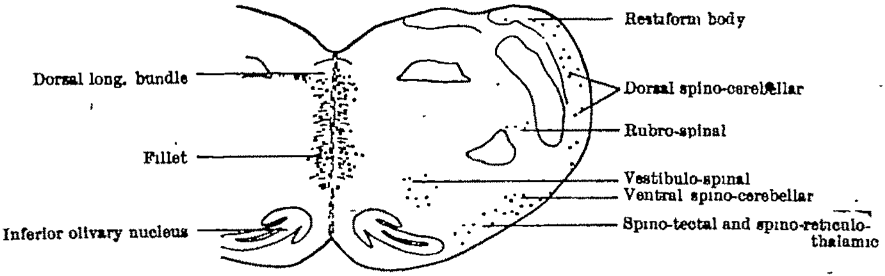

FIG. 16.—Medulla, level of inferior olivary nucleus and 4th ventricle.

Drawings illustrating degeneration in brain-stem and spinal cord of a rabbit on a carotene-deficient diet.

evidence of degeneration in a third neuron has been found either in this rabbit or in any others of the series so far examined.

Medulla, lower part of sensory decussation (rabbit B) (fig. 14).—Ascending degeneration is seen in the fillet, in the ventral spino-reticulo-thalamic tract, in the dorsal and ventral spino-cerebellar tracts, in the lateral spino-reticulo-thalamic, in the spino-tectal and possibly the spino-olivary tracts. Descending fibres in the dorsal longitudinal bundle, the vestibulo-spinal and the rubro-spinal tracts are degenerated. At this level the dorsal longitudinal bundle and the vestibulo-spinal tract can be seen in separate bundles, while in the cord they could not be clearly differentiated from other tracts.

Medulla, level of the inferior olivary nucleus (below 4th ventricle) (rabbit B) (fig. 15).—In this section there is much degeneration in the fillet and also some in the dorsal spino-cerebellar tracts, but less than in rabbit A. The ventral spino-cerebellar, spino-reticulo-thalamic and spino-tectal tracts contain some degenerated fibres which are seen in the same positions as in fig. 8. Degenerated fibres of the vestibulo-spinal tract appear dorsal to the inferior olivary body. The dorsal longitudinal bundle and the rubro-spinal tracts containing degenerated fibres retain the same relative positions. There is no degeneration in the pyramids. So far, degeneration has not been found in the 12th, 11th, 10th or 9th nerves.

Medulla, level of inferior olivary nuclei and 4th ventricle (rabbit B) (fig. 16). Degenerated fibres of the mesial fillet are the most prominent features of this section, degeneration being heavier than in any other of the ascending tracts. The dorsal spino-cerebellar, ventral spino-cerebellar, spino-reticulo-thalamic and spino-tectal tracts contain some degenerated fibres. The dorsal longitudinal bundle and vestibulo-spinal tracts are the most severely degenerated of the descending fibres, but the descending vestibular root and the rubro-spinal tracts are also affected. In contrast to fig. 9 (rabbit A) there are no degenerated fibres among the cells of the lateral reticular nucleus. The pyramids are again without degenerated fibres.

Level of 8th nerve (rabbit B) (fig. 17).—This section shows degenerated ascending fibres in the fillet, restiform body, spino-reticulo-thalamic, ventral spino-cerebellar and spino-tectal tracts. Degenerated descending fibres are seen in the dorsal longitudinal bundle, vestibulo-spinal and rubro-spinal tracts. The pyramids are again unaffected. Roots of the 8th and 7th nerves can be seen and many degenerated fibres are present in the former, but none in the latter.

Pons, 5th nerve level (rabbit B) (fig. 18).—Degeneration can be seen in the regions of the spino-reticulo-thalamic and spino-tectal tracts. The degenerated fibres of the restiform body have disappeared, and the degenerated ventral spino-cerebellar tract is now coursing towards the superior cerebellar peduncle. Degenerated fibres can be seen in the dorsal longitudinal bundle and what are presumably the rubro-spinal and vestibulo-mesencephalic tracts. The pyramids are again free from degeneration. Degeneration can be clearly seen in the fibres of the 5th nerve.

Posterior part of superior corpora quadrigemina (rabbit B) (fig. 19).—Much less degeneration is present in this section than in fig. 18. No degeneration is

RABBIT B.

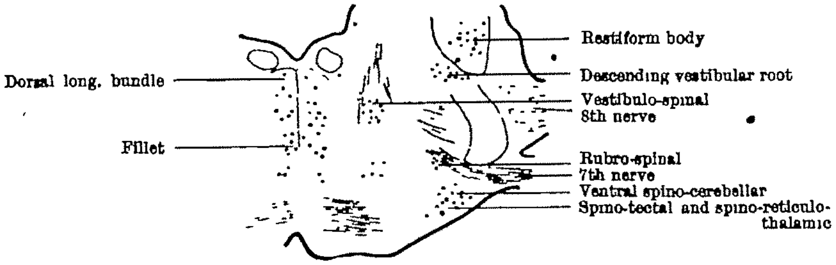

FIG. 17.—Level of 8th nerve.

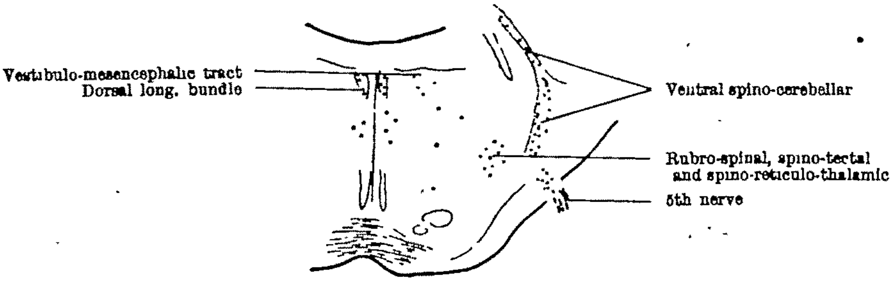
Vestibulo-mesencephalic tract
Dorsal long. bundle
Ventral spino-cerebellar
Rubro-spinal, spino-tectal and spino-reticulo-thalamic
5th nerve

FIG. 18.—Pons, 5th nerve level.

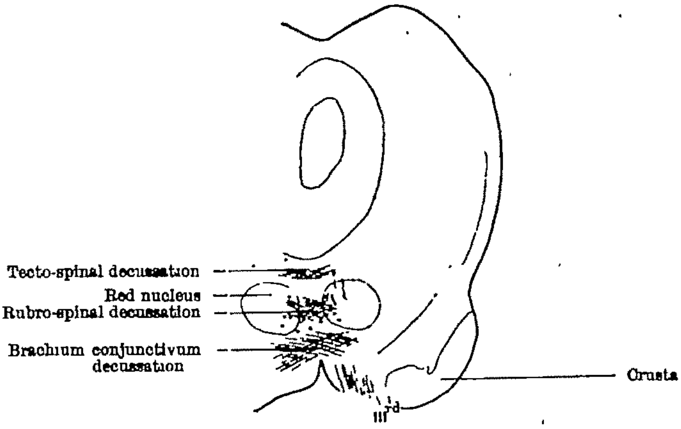

FIG. 19.—Posterior part of superior corpora quadrigemina.

Drawings illustrating degeneration in brain-stem and spinal cord of a rabbit on a carotene-deficient diet.

seen in the ascending tracts of this region, as they have probably entered relay stations. Degenerated fibres are present in the dorsal longitudinal bundle and in the decussation of the rubro-spinal tract.

DEGENERATIVE CHANGES IN PERIPHERAL NERVES.

Extension of the investigation to the peripheral nerves was begun because the inco-ordination of the animals, and especially the movements of the head, often appeared greater than might be expected from the extent of lesions of the central nervous system. For this reason the vestibular divisions of the 8th nerve were first examined and it soon became obvious that this nerve suffered greatly in the animals receiving the carotene-deficient diets. This is illustrated in Plate IV, fig. 1. Not only are the extra-medullary parts of these nerves degenerated, but intra-medullary fibres are also affected. (Plate V, fig. 1.) The degeneration in the 8th nerve accounts largely for the inco-ordination of the head movements so often seen in carotene and vitamin A deficient animals. Fig. 2 shows the normal when cabbage was included in the diet.

The cochlear division of the 8th nerve was then examined, and here again changes were revealed, which are illustrated in Plate IV, figs. 3 (*a*) and (*b*). It will be seen that while the rabbit receiving carrots (figs. 4 (*a*) and (*b*)) has a normal nerve, that of the carotene-deficient animals contains fibres with extensive myelin changes (figs. 3 (*a*) and (*b*)). Similar differences were also seen in that part of the cochlear nerve which passes through the cochlear bone. Preparations were made after decalcification of the bone. A point of special interest is the round-cell infiltration within the bony cochlear found in the carotene-deficient animal and the absence of these cells from the control. The results obtained leave little doubt that the cochlear nerve is very susceptible in these young rabbits to the special nutritional defect under examination.

Degenerating fibres were also found in the optic nerves of the carotene-deficient animals (Plate V, figs. 3 and 4). I have shown elsewhere [1 (*b*)] that these changes were sometimes so severe in dogs which have been fed for several years on a vitamin A and carotene-deficient diet that all the fibres of the optic nerve have disappeared. This aspect of the subject I propose to deal with at greater length in another publication because of its possible relationship to retrobulbar neuritis and night blindness, the latter a well-recognized result of vitamin A and carotene deficiency.

The other sensory nerve of the eye—the ophthalmic division of the trigeminal nerve—has been discussed in full previously, more particularly in relation to xerophthalmia [1 (*e*)]. It was there shown that degeneration of this nerve and xerophthalmia are associated, and that the latter can probably be regarded as due to a loss of neurotrophic control.

It is evident that these investigations on the optic and trigeminal nerves, by supplying a common basis in the form of afferent nerve defect due to a specific dietetic deficiency, offer an explanation for two pathological conditions affecting the eye, night blindness and xerophthalmia, two conditions which at first sight seem to have no relation to one another.

One other sensory nerve of the head, namely, the inferior dental nerve, has also been the subject of inquiry by M. Mellanby and J. D. King [6], who have shown that vitamin A and carotene deficiency bring about, in young rats, dogs and rabbits, degenerative changes in it. They also found evidence that these demyelination changes were related to hyperplasia of the epithelium of the gum margin, especially of the part adjacent to the teeth, and the subsequent invasion of the epithelial cells by micro-organisms resulting in pyorrhœa, a disease which develops in animals eating a cereal diet deficient in vitamin A and carotene [7].

Thus it is evident that all the sensory nerves of the head so far examined in young rabbits are affected by carotene deficiency, including both auditory and vestibular branches of the 8th nerve, sensory branches of the 5th nerve to the eyes and teeth and the optic nerve. On the other hand the motor cranial nerves were normal in the experiments so far completed at a time when the sensory nerves of the head showed great demyelination changes; a few degenerated fibres, however, have been occasionally seen in the 3rd nerve (fig. 12).

In view of the almost clear-cut division between the susceptibility of the sensory and motor cranial nerves, it was a matter of interest to see whether other afferent and efferent nerves behaved similarly under these dietetic conditions. Sciatic nerves which contain both efferent and afferent fibres are affected by carotene deficiency (compare figs. 5 and 6 of Plate V). On the analogy of the cranial nerves it seemed likely that the afferent fibres would be affected and that the motor fibres would escape. This is the case in the majority of the experiments for, in the rabbits brought up on carotene-deficient diets and showing typical signs of the deficiency, the ventral roots (motor) were usually free from myelin degeneration, whereas the dorsal roots were always affected (Plate VI, figs. 1 to 4). Both roots of the animal fed on cabbage are devoid of degeneration, whereas in the animal not receiving carotene the dorsal root shows much degeneration, whilst the ventral root is normal. This is the usual result, but in animals where the dietetic defect has continued for a long time some of the ventral root fibres also may be degenerated. The affection of the dorsal roots can be clearly demonstrated by Cajal's osmic method (Plate VI, figs. 5 and 6). When the rabbit had the basal diet only, the degenerative changes are obvious (fig. 5), but when a few drops of concentrated vitamin A oil (0·1 c.c. = 100 blue values), were added to the diet the fibres are normal (fig. 6).

Reference has been made above to the vagus nerve. It might be expected that, although the motor fibres in this nerve would escape, its afferent fibres would suffer in the same way as most of the other afferent nerves. This has not been found to be true; in spite of many examinations of these nerves, even in severely affected animals, no degenerative changes have so far been seen in them. In rats brought up on a vitamin A deficient diet, Zimmerman [8] found some degeneration in the vagus nerves in only four out of eight animals examined, but in all there was extensive degeneration of the medullary sheaths of the brachial plexuses and sciatic nerves.

There is still a wide field left for future observation as regards these nerve changes. It is known that both the skin and epithelial surfaces are particularly susceptible to infection in vitamin A deficiency, and epithelial surfaces also develop characteristic changes as hyperplasia and keratinization of their cells. On the analogy of the eye (xerophthalmia) and the gums (periodontal disease) it is probable that these epithelial changes are related to degeneration of the corresponding afferent nerves. It would be of interest to know whether the afferent nerves from joints and muscles are also affected by the dietetic deficiency under examination, and, if they are so affected, whether specific lesions are produced in these end organs which correspond to the pathological changes developing in the skin and epithelial surfaces.

NERVE-CELLS.

In view of the great degenerative changes in the conducting fibres of the cord resulting from these specific nutritional defects, it is not surprising that many cells are also affected. Indeed, it is not improbable, considering the differentiation between the widespread degeneration of the intermedullary ascending fibres and the afferent nerves and the comparative immunity of the descending tracts and the efferent nerves, that many of the primary effects of the abnormal nutrition under consideration are on the cells and that the changes in the nerve fibres are secondary.

In spite of the large amount of work done by many investigators on the morbid anatomical changes of nerve-cells, there still remains a general lack of systematized knowledge as to the relation of the structures seen under the microscope after fixation and other treatment and their functional state during life. Nissl's bodies found in suitably stained sections vary in size, shape and arrangement in the different nuclei of any one species, and in different species cells having the same functions often vary greatly in appearance. This introduces a difficulty into the interpretation of experimental results even when care is taken to use controlled and efficient methods of fixation and to avoid post mortem and manipulative changes. However, when all technical errors in preparation have been avoided and all the processes are carried through as far as possible under identical conditions, there is no doubt at all that there are greater differences in the microscopical appearances of the nerve cells of the carotene-fed and carotene-free animals than can be accounted for by normal variations.

When nerve-cells undergo degenerative changes as the result of lesions of their axons, the process is usually called secondary degeneration. Cell changes brought about by toxic agents are known as primary degenerations. This phraseology was introduced by Marinesco.

Secondary degeneration of the nerve-cell due to injury of its axon, and particularly the changes in the chromophile elements, was discovered by Nissl [9]. It consists of a breaking up of the chromophile elements first beginning round the nucleus, a swelling of the whole cell and a movement of the nucleus towards the periphery. All nerve-cells whose conducting fibres are cut do not react in this way. The best reactions are seen in motor cells, as those of the ventral horns or in the cortical motor cells, when their respective conducting fibres suffer transection. Peripheral afferent nerve-cells, as those of the dorsal root ganglion, undergo secondary degeneration when the peripheral portions of the fibres are divided, but not when their central processes, i.e. the dorsal roots, are injured.

In the central nervous system itself, apart from the chromolysis and other changes seen in the cells of Clarke's column when the dorsal spino-cerebellar tract is destroyed, but little is known of secondary cell changes in ascending systems. It is certain, however, that afferent cells in the central nervous system are by no means as susceptible to this type of change as the motor cells.

The question of primary or toxic reactions of nerve-cells, the so-called primary degenerations, is even more complex. Since the introduction of the Nissl technique, many investigations have been made to determine the changes produced in nerve-cells by known toxic substances. Nissl [11] himself investigated the action of many such substances including lead, arsenic, phosphorus, mercury, silver, alcohol, morphine, bromide, cocaine, trional, veratrine, strychnine, carbon disulphide, and tetanus toxin. Goldscheider and Flatau [12] also made many investigations into the effect of pathological conditions produced experimentally on nerve-cells. Russell [13] has studied the effect of parathyroidectomy on cells of the nervous system, and in more recent times Dye [14] has compared the effect of parathyroidectomy and cretinism on the nerve-cells of dogs. Other harmful procedures whose effects on nerve-cells have been studied include ischæmia, inanition, hyperpyrexia, uræmia, extirpation of the suprarenal bodies, and experimental and natural infection.

Although it is undoubted that nerve-cells undergo changes under many of the above conditions, the subject of primary degeneration has remained generally unsatisfactory and undeveloped. One of the difficulties in work of this nature is, as Nissl himself recognised, that under conditions which produce primary degeneration of the nerve-cells even one group may show the widest variations, some appearing nearly normal and others having great degenerative changes. Even in normal animals the cells in one group may vary in their appearance. In his studies of the effect of parathyroidectomy and cretinism on the nerve-cells of dogs, Dye [14] met the same difficulties. He found that chromolytic reaction in nerve-cells follows the same general course in conditions of such diverse symptomatology as parathyroid tetany and cretinism, and decided that chromolysis is a reaction of nerve-cells initiated by any factor which opposes the normal physiological equilibrium of these units, a conclusion similar to that reached years ago by Van Gehuchten.[1]

In primary degenerative changes, as pointed out by Van Gehuchten [15], the Nissl bodies or chromophile particles do not, as a rule, undergo real chromolysis. When altered in this direction there is no real dissolution of the chromophile substance, but rather an achromatosis or partial disappearance or change of chromophile elements in some part of the cell. Marinesco states that, when the lesions are primary, chromolysis commences in the periphery of the nerve-cells and spreads towards the centre, whereas in secondary or traumatic degeneration the chromolysis begins centrally and spreads towards the periphery.

In the present investigations the changes in the nerve-cells can be classified among the primary or toxic group, although produced by ordinary foodstuffs without the addition of any known toxic agent. On the whole, but not absolutely, Marinesco's generalisation as to the peripheral location of changes in the Nissl bodies in primary degeneration applies to the present results, although there are some exceptions. Real chromolysis (in the sense used by Nissl) is not very common, and when present generally affects a small portion of the cell either at the periphery or near the nucleus. A few instances of chromolysis comparable to that seen in secondary degeneration were found, more especially in certain cells of the medulla. More often the granules lose their discrete form and are in a powdery or lightly staining condition, the parapyknomorphic change of Nissl. At times the Nissl bodies may be aggregated into clumps, and in other cases they may be so changed that the cell takes on a more intense, even stain and is described as chromophile.

In addition to degenerative changes in the cytoplasm, the nucleus and nucleolus are often affected. They may be swollen or shrunken. Sometimes the nucleus leaves the centre of the cell and becomes eccentrically placed. Occasionally the nucleus seems to have disappeared or its space to be invaded by the cytoplasm with Nissl bodies. At times the nucleus may appear finely granular instead of clear as it is normally.

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[1] For discussions of the various hypotheses concerning chromolysis in damaged nerve cells *see* Van Gehuchten, *Anatomie du Système Nerveux, de l'homme*, 1900, Vol. 1, pp. 318-339; also S. Ramon-y-Cajal, *Histologie du Système Nerveux*, 1909, Vol. 1, pp. 214-222.

If any one of these abnormalities appeared in a group of nerve-cells the problem of description would be relatively simple, but the fact is that in any group of cells in a single animal many of these appearances can be detected in different cells. Even in the control animals, where the diet contains abundant carotene and the condition of the animals is excellent, a few of the cells will often appear abnormal. Thus it often happens that, although the observer feels fully assured that the experimental condition under investigation has produced degenerative changes in particular groups of nerve-cells, when he comes to describe these it is a matter of great difficulty.

The following brief description of changes in nerve-cells that are produced by diets high in cereals and deficient in carotene is given not so much because of any claim to finality, but rather to introduce an aspect of nerve-cell pathology which is easily producible experimentally and which, because of its probable significance in man, is worth more detailed study, for it will be generally agreed that a pathological condition of the nervous system which can be produced by ordinary foodstuffs is an important field of investigation.

The chief fixatives used for nerve-cells were 10 per cent. neutralized formol saline and Carnoy's solution (Perdrau's modification). Of these Carnoy's gave the better results owing to more rapid penetration due to the presence of acetic acid, the subsequent staining being deeper and sharper as well as more lasting.

The stains employed for demonstrating the changes seen in nerve-cells include: methylene blue (polychrome), toluidene blue and the Unna-Pappenheim stain (pyronin and methyl green). Silver impregnation methods have so far been little used in these experiments although there are indications that such methods would give interesting results.

CHANGES IN NERVE-CELLS.

Dorsal root ganglia (Plate VII, figs. 1 to 7).—In the dorsal root ganglia there are normally two types of cells, the larger staining rather faintly and the smaller more strongly. The most representative change in these ganglia in carotene-deficient animals is the powdering and loss of defined granules in the main body of the cell and the apparent concentration of granules around either the nucleus or the outer edge. The only obvious differences between degenerated large and small cells is that the small cells seem to be more affected by the "piling" reaction, but this may be more apparent than real owing to their deeper staining. This "piling" of the granules around both the nucleus and the outer edge has been seen in the same cell, but it is most common to find the chromophile substance concentrated around the nucleus. Eccentric nuclei have also been found. The nuclei of the capsule or, according to Cajal, the sub-capsule, have sometimes proliferated around degenerate cells, giving by Nissl's method a picture akin to what has been called "neuronophagia" in the cells of the central nervous system.

Gasserian ganglia.—Changes in the cells of the Gasserian ganglion are also seen in the carotene-deficient animals. These include eccentric nuclei, proliferation of the nuclei of the cell capsule, powdery granules and "piling" of the granules around the nucleus and at the outer edges of the cell, the latter being very distinct. ("Piling" appears to be less obvious in cells of the central nervous system than in those of the dorsal root and the Gasserian ganglia, which are the only cells of the peripheral nervous system so far examined).

Clarke's column and other dorsal horn cells (Plate VIII, figs. 1 and 2.)—These cells are rather small, and even in the normal the granules are not clearly defined. There are, however, undoubted differences between the animals with and without carotene. In advanced cases of carotene-deficient diets some cells seem to have disappeared, leaving only a skeleton behind, but loss of granules without other apparent change is common. In less severe cases neuronophagia, loss of definition of the granules and eccentric and slightly granular nuclei are the usual changes.

Lateral horn cells.—No striking changes have so far been noted in these cells.

Ventral horn cells (Plate VIII, figs. 3 and 4).—The large motor cells are usually entirely free from degeneration; occasionally, however, in advanced cases of vitamin A deficiency, clumping of the granules and even slight chromolysis, is found.

Nuclei gracilis and cuneatus.—The cells of these nuclei fall into line with the other cells of the afferent paths. Eccentric nuclei, powdery granules and loss of granules being seen in carotene-deficient animals, whilst in those on a carotene-containing diet they remain normal.

Lateral reticular nucleus (Plate VIII, figs. 5 and 6).—Powdering and loss of granules, clouding of the nucleus, eccentric nuclei and neuronophagia are the usual changes in the carotene-deficient animals. These groups of cells are usually only badly affected when there is much degeneration in the lateral columns of the cord and in the restiform body (see also p. 164, R. Cajal and and V. Gehuchten).

Olivary nucleus.—This nucleus receives sensory fibres from the ventral columns. Even in animals on the carotene-containing diets cells of the olivary nucleus with clearly defined granules seem to be rare. Eccentric nuclei have been found in cells of animals on a carotene-deficient diet and this seems to be the main difference from control animals.

Hypoglossal nucleus.—There are no definite differences in these nuclei between animals on carotene and carotene-deficient diets.

Nucleus solitarius (position rather more dorsal than in man).—This nucleus, which receives afferent branches from the facial, glossopharyngeal and vagus nerves, is often severely affected. The cell changes are powdering and loss of granules, frequently with eccentric nuclei. Some of the cells in this nucleus in two or three carotene-receiving animals appear to be slightly degenerated compared with those considered as normal.

Nucleus ambiguus.—In this nucleus changes have been noted in the experimental animals. Powdering of the granules is by far the most common change, but eccentric nuclei have been seen; in a few carotene-deficient animals showing definite changes in many other nuclei no abnormalities have been seen in this group of cells. In the animals receiving carotene no degenerated cells have been found.

Vestibular nuclei (Plate VIII, figs. 7 and 8).—In carotene-deficient animals changes in the lateral and medial vestibular nuclei are seen regularly, the cells of the latter appearing most severely affected. Powdering of granules, eccentric nuclei and neuronophagia are the common changes, but in advanced cases many remnants of degenerated cells are also found. Cells of the control animals are normal.

Facial nerve nucleus (*7th*).—These cells are large and usually have well-defined nuclei and Nissl granules in both carotene and carotene-deficient animals. Degenerative changes have been found in some cells in two out of the ten facial nuclei of the deficient animals examined, but none in the carotene-fed rabbits.

Abducens and accessory 6th nuclei.—Few cells of these nuclei have been examined, but no differences between those in the animals with and without carotene have been observed. The slight changes seen in one case were within what are probably the normal limits.

Descending 5th nucleus.—Changes are usually seen in the small cells of this nucleus in the affected animals. In some advanced cases they appear to have been entirely destroyed, but powdery granules and eccentric nuclei can be found in most experiments in which the animal's diet did not contain carotene.

Oculomotor nucleus (Plate IX, figs. 1 and 2).—This nucleus, even in the control animals, contain cells which appear to be abnormal; more of these are seen in the carotene-deficient animals, and in one or two cases extensive degeneration was present.

Red nucleus (Plate IX, figs. 3 and 4).—Clumping of the granules is the most obvious change in the cells of this nucleus in the carotene-deficient animal. The granules appear larger and more widely scattered and have no definite arrangement as in the normal. Powdery granules have also been found fairly regularly, but on the other hand eccentric nuclei and neuronophagia have been so far rarely seen.

Purkinje cells (Plate VII, figs. 5 and 6).—Purkinje cells of the cerebellar cortex in rabbits receiving carotene are flask-shaped and have a large nucleus with a nucleolus situated towards the base of the flask. The protoplasm is normally granular and around the nucleus has a deeply staining demilune appearance. Of all the groups of cells examined in this work these show perhaps the most consistent changes. In the well-established cases of carotene deficiency it is rare to see many Purkinje cells in which some change is not apparent. The nucleus becomes cloudy and can often only be recognized by means of the nucleolus, the demilune merges into the rest of the protoplasm and cannot be differentiated, the cell edges become frayed and sometimes, although the whole cell stains deeply, granules cannot be distinguished.

Dentate nucleus.—These cells in the carotene-deficient animals do not as a rule show such severe changes as the Purkinje cells, but loss of definition of the nucleus and powdery granules are often found.

Other groups of cells (Plate IX, figs. 7 and 8).—Here are included the medial accessory olivary nucleus and cells scattered in the median raphe, especially in the medulla. Many cells showing the changes described above are seen, but intense chromolytic changes such as are found when the axon of a motor cell is cut were obvious in some cells. These are the cells referred to on page 164 as exceptional in their reactions. Their appearance, in contrast with most other cells examined in this investigation, would suggest trauma of their conducting axon.

DISCUSSION.

The foregoing account describes some of the changes in the central and peripheral nerve-fibres, and in the central and peripheral nerve-cells which can be readily produced in young rabbits by diets rich in cereals and deficient in carotene and vitamin A. Only the anatomical changes in relation to the general behaviour of the affected animals have been dealt with here. The experimental development of the study and its clinical significance I have discussed elsewhere [1 (*a*) (*b*) (*c*) (*d*) (*e*) (*f*)]. There [1 (*c*) (*d*) (*f*)] I have indicated a probable relationship between various diseases of the nervous system and diet which further work will no doubt expand. There is, for instance, good evidence that in some of the so-called toxic degenerations, especially those associated with restricted diets as convulsive ergotism, pellagra and lathyrism, a deficient intake of vitamin A and carotene is of ætiological significance. In subacute combined degeneration of the cord, the evidence is not so good, but it is difficult to escape the conclusion, not only that this disease is nutritional in origin, but that the responsible defect involves a biochemical mechanism in which vitamin A is concerned. Even in disseminated sclerosis there is suggestive evidence that a diet rich in vitamin A and other protective food factors increases the resistance of the nervous system to the toxic agent at fault, and that such a diet can improve the clinical condition of early acute attacks of this disease and possibly check the rate of advance in more established chronic cases.

It is necessary to emphasize that the investigations here described and the interpretation of the results must only be regarded as of a preliminary nature; it is for neurological experts to develop the subject which is essentially one of toxic degeneration of the nervous system produced by ordinary foodstuffs and the protective effect of other specific substances. The fact that the same kind of degenerative changes can be experimentally produced by dietetic means in dogs and rats, together with the fact that morbid conditions of a comparable nature are found in man, show the subject to be one of both scientific and practical interest. The work emphasizes the importance of the specific relation of nutritional substances to the structure and proper action of the whole nervous system. Possibly the results may prove of even greater significance; the fact that degenerative changes are more easily produced in young than in old animals suggests that these same nutritional factors play a large part in determining the structural development of the nervous system, either as a whole or in part, in early life and even in the fœtus. If this is so, it is another instance of the supreme importance of the proper nutrition of the mother during pregnancy and lactation, and of the young child during the development of the nervous system.

I have already mentioned the difficulty of producing lesions in the adult animal by diet. Until recently I had not succeeded in either rabbits or dogs. Lately, however, some success in this direction has been obtained, but an account of this work I shall leave to a later publication. Suffice it to say that the intensity of the degenerative changes has not approached that described in this paper when young animals were investigated. In adult animals the amount of demyelination of fibres and the lesions in the nerve cells of the central nervous system are relatively small. There is some evidence that, apart from a deficiency of vitamin A and carotene and excess of cereal, some other nutritional defects aid in the production of degenerative lesions in the nervous system of adult animals. It would in fact appear that vitamin A bears the same kind of relation to the nervous system as vitamin D bears to bone and teeth structure. Had the experiments which led to the discovery of vitamin D been begun on adult animals, the successful issue would have been greatly delayed; for although osteomalacia in adult animals or man is clearly comparable to rickets in early life, this disease does not develop when vitamin D insufficiency is the only dietetic defect as rickets does in infants. It is possible that the difficulty of producing nerve lesions in adult animals by vitamin A or carotene deficiency is due to the fact that vitamin A controls some form of metabolism and works in conjunction with other dietetic elements in a way comparable to the interaction of vitamin D with calcium and phosphorus. Further work will have to be done before this question is settled. It can be said with assurance, however, that the adult nervous system is much more stable under the experimental conditions employed than that of young animals and that it is more difficult to produce nervous degeneration by defective diets.

It may be asked, does this work provide any solution to the question as to whether the nerve-cell or its conducting fibre is first influenced by the special dietetic conditions used? No definite answer can be given. It was hoped that the results of experimental studies of secondary (traumatic) degeneration might throw some light on this problem. Conducting fibres when cut off from their nerve-cells degenerate, but only in certain nerve-cells does chromolysis appear. For instance, motor-cells of cerebral nerves always react in this way, while spinal anterior horn cells sometimes show chromolysis after simple section of their axis cylinders, while in other cases severer injury of their conducting fibres is necessary to produce the typical change. Again, many of the afferent nerve-cells seem to remain normal, or at least escape sufficiently great change to be demonstrated by histological methods in general use, after injury of their conducting fibres, e.g. the posterior root ganglion cells after section of the posterior roots, also the ganglion of the vagus after section of the nerve central to the ganglion (van Gehuchten [16]). Thus it would seem that nerve-fibres can in some cases be damaged without the nerve-cells undergoing obvious degenerative changes, and that this applies specially to nerve-cells and fibres of the afferent system.

Recent work of Sherrington [17] has shown on the other hand that motor nerve-cells can show changes of degeneration without their conducting fibres being structurally damaged. In his recent experiments total spinal transection in the dorsal region of the cord of monkeys produced chromolysis in a number of motor horn cells in the hind-limb region, e.g. in the 5th lumbar segment. However, the motor fibres arising from chromolysed cells which supply the tibialis anticus, the anterior longus digitans and gastrocnemius failed to show any degeneration even seventeen days after spinal transection. It is clear that nerve-cells can show chromolysis and yet their conducting fibres escape obvious myelin degeneration. It is interesting to note that, although these fibres appeared normal in structure, evidence was obtained which indicated that they were not normal in function (Sherrington [17], and Fulton and Sherrington [18]. Thus the contraction of the innervated muscle in response to a single shock stimulus was of subnormal tension value and very sluggish as compared with the response of the same muscle in a normal animal. Sherrington calls this type of reaction " transneuronal degeneration."

So far, then, the evidence of traumatic degeneration indicates that spinal motor nerve-cells may be either normal or abnormal when the conducting fibres are degenerated, that the nerve-fibres may appear normal when their corresponding cells show chromolysis and that, in the case of some afferent nerve units, the cells may escape chromolysis when the conducting fibres are degenerating. It is evident that these results of trauma offer no aid to the solution of the problem as to whether the primary lesion in experiments described in this paper is in the nerve-cell or its conducting fibre.

At one period of the work, when the démyelination changes in nerve-fibres seemed to be the outstanding effect of vitamin-A deficiency, H. N. Green [19], working in my laboratory, endeavoured to find out whether vitamin A had some special relationship to fat metabolism. If this had been established, it might have afforded some support for the view that the nerve-fibre, and especially its myelin covering, was primarily involved in vitamin A deficiency. However, there was no evidence of any specific relationship between vitamin A and fat metabolism.

There is, as indicated above, a good deal of specificity in the nerve cells and fibres affected, the afferent system being on the whole much more liable to change than the motor system. This might be regarded as evidence that the nerve-cell lesion is primary because it seems more likely that specificity of reaction would be shown by nerve-cells than nerve-fibres. It may be possible to settle this question in the adult animal, for early observations indicate abnormality of the cell without any obvious change in its conducting fibres. Thus in one adult animal the ganglion cells of the retina are degenerating and show chromolysis while there is no obvious myelin degeneration in the optic nerve.

In their biochemical aspect these experiments have a particular interest, especially in view of earlier and contemporary work showing the close interaction between specific chemical substances and the nervous system. I refer particularly to the recent work by Dale and his colleagues [20 and 21] on acetyl choline in relation to nerve-endings and nerve-cell activity, and to the earlier investigations which established the close relationship between adrenaline and most sympathetic nerve-endings (Elliott [22]). It would appear indeed that a new stage of biochemical knowledge regarding nervous tissue is opening up, and that the time is not far distant when there will be much more information available about the physiological action of specific chemical substances in controlling the normal structure and function of nervous tissue. It has long been known that the nervous system is specially susceptible, and gives specific responses, to many drugs of plant origin, and it might, therefore, be expected that this system would also be controlled by chemical agents with a drug-like action which are, however, physiological and present in the body. Modern investigations, including the present work, show that this is certainly the case and that the field is one of great promise.

SUMMARY.

(1) A diet is described deficient in carotene and vitamin A which allows young rabbits to grow until abnormal movements and general behaviour indicate widespread pathological changes in the nervous system which can be demonstrated post mortem.

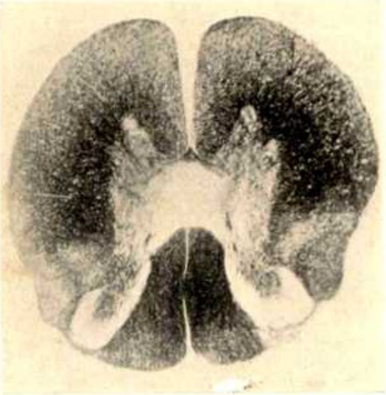
(2) The daily addition of 1 to 3 mgm. of pure carotene, or of some source of carotene (carrots, cabbage, &c.), to this basal diet prevents the development of these lesions of the nervous system. Vitamin A has the same protective effect.

(3) Generally speaking, it is the afferent side of the nervous system which is specially affected, but so far degenerative changes have only been found in the first and second neurons. All the afferent nerves of the head examined, including the optic nerve, the sensory fibres of the 5th, and the auditory and vestibular fibres of the 8th, suffer greatly. The motor cranial nerves usually escape, but some degeneration has occasionally been found in the 3rd nerve. In the body the same rule holds, the degeneration affecting primarily the dorsal root-fibres, those of the anterior roots remaining normal except when the nutritional deficiency has been very prolonged. No degeneration has been seen so far in the vagus nerve, even in its afferent fibres.

(4) A description of the distribution of myelin degeneration in the nerve-fibres and tracts inside the nervous system at different levels is given. Here, again, the fibres affected are mostly ascending and include the dorsal and ventral spino-cerebellar, the dorsal and ventral spino-reticulo-thalamic tracts, and the tracts of the dorsal columns. Some descending tracts suffer change, including the rubro-spinal, the dorsal longitudinal bundle and the vestibulo-spinal, all of which are associated with the mid-brain or medulla. The pyramidal tract generally escapes in the rabbit under these nutritional conditions.

(5) Degenerative changes of different degrees are seen in nerve-cells as well as in their conducting neurons; a description is given of the histological appearance of many such cells both in the central and

PLATE III.



Photomicrograph of section of high cervical cord, rabbit B, stained by hæmatoxylin after mordanting. Pale areas show complete loss of many fibres.

To illustrate paper by Edward Mellanby.

PLATE IV.

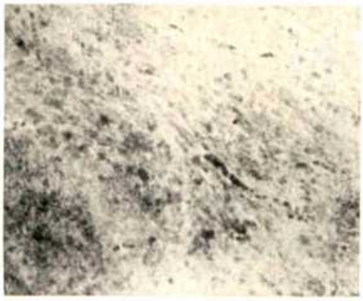


FIG. 1.

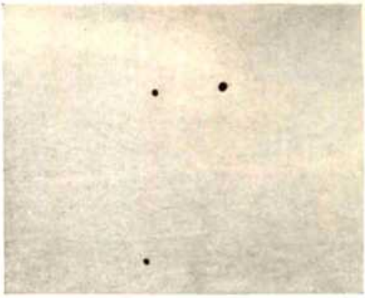


FIG. 2.

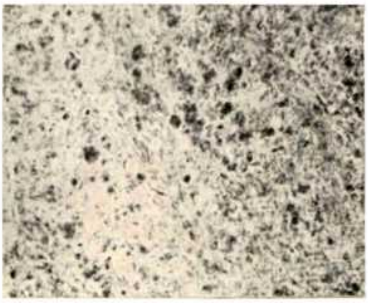


FIG. 3*a*.

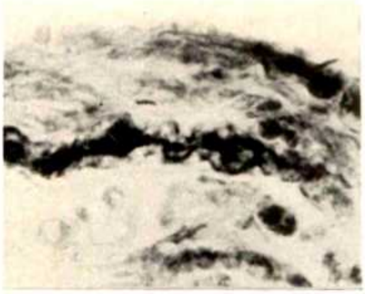


FIG. 3*b*.

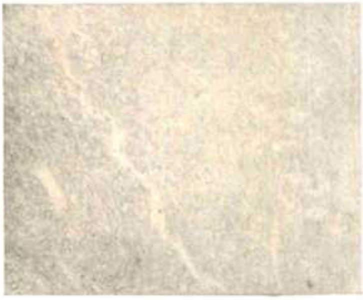


FIG. 4*a*.

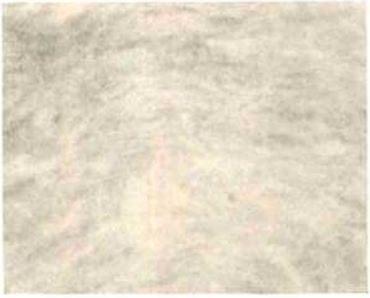


FIG. 4*b*.

FIG. 1.—Vestibular division of 8th nerve, diet deficient in carotene and vitamin A. Marchi stain × 280.

FIG. 2.—Vestibular division of 8th nerve, diet contained cabbage. Marchi stain × 280.

FIG. 3*a*.—Cochlear division of 8th nerve, diet deficient in carotene and vitamin A. Marchi stain × 280.

FIG. 3*b*.—Cochlear division of 8th nerve, diet deficient in carotene and vitamin A. Marchi stain × 750.

FIG. 4*a*.—Cochlear division of 8th nerve, diet contained carrot. Marchi stain × 280.

FIG. 4*b*.—Cochlear division of 8th nerve, diet contained cabbage. Marchi stain × 750.

(In this and the following plates the photomicrographs were reduced by one quarter in reproduction.)

Photomicrographs illustrating 8th nerves (vestibular and cochlear divisions) in rabbits, with and without carotene and vitamin A.

To illustrate paper by Edward Mellanby.

PLATE V.

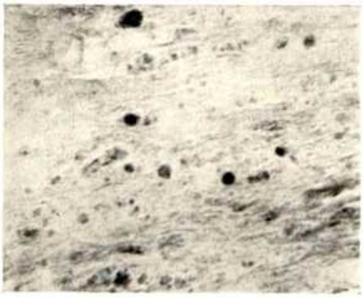


FIG. 1.

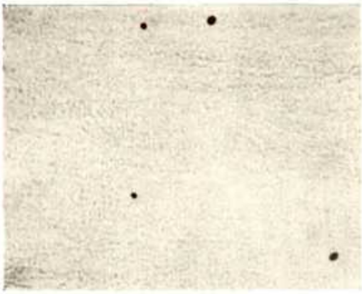


FIG. 2.

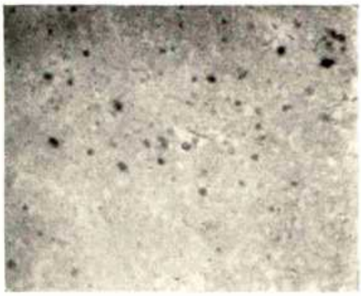


FIG. 3.

FIG. 4.

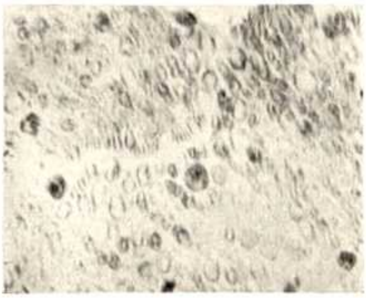


FIG. 5.

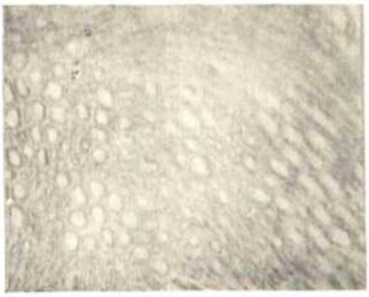


FIG. 6.

FIG. 1.—Intramedullary 8th nerve, diet deficient in carotene and vitamin A. Marchi stain × 280.

FIG. 2.—Intramedullary 8th nerve, diet contained pure carotene. Marchi stain × 280.

FIG. 3.—Optic nerve, diet deficient in carotene and vitamin A. Marchi stain × 280.

FIG. 4.—Optic nerve, diet contained carrot. Marchi stain × 280.

FIG. 5.—Sciatic nerve, diet deficient in carotene and vitamin A. Marchi stain × 280.

FIG. 6.—Sciatic nerve, diet contained cabbage. Marchi stain × 280.

Photomicrographs illustrating intramedullary 8th nerve, optic and sciatic nerves in rabbits, with and without carotene and vitamin A.

To illustrate paper by Edward Mellanby.

PLATE VI.

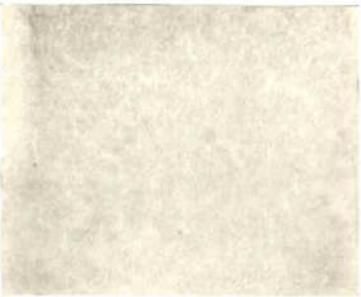


FIG. 1.

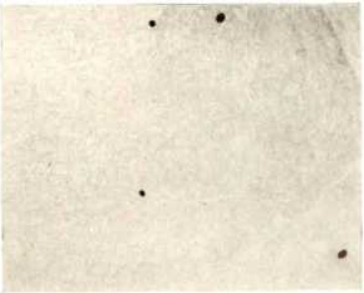


FIG. 2.

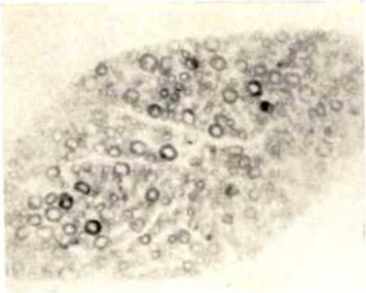


FIG. 3.

FIG. 4.

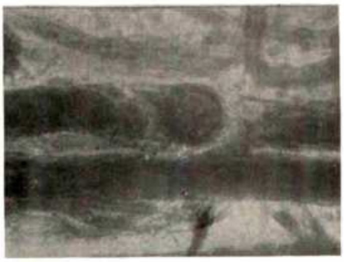


FIG. 5.

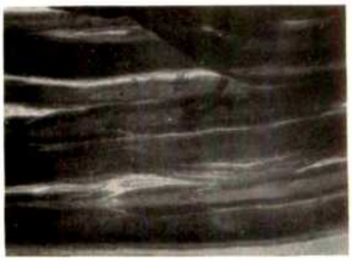


FIG. 6.

FIG. 1.—Ventral root, diet deficient in carotene and vitamin A. Normal. Marchi stain × 280.

FIG. 2.—Ventral root, diet contained cabbage and carrot. Normal. Marchi stain × 280.

FIG. 3.—Dorsal root, diet deficient in carotene and vitamin A. Annular degeneration. Marchi stain × 280.

FIG. 4.—Dorsal root, diet contained cabbage and carrot. Normal. Marchi stain × 280.

FIG. 5.—Dorsal root, diet deficient in carotene and vitamin A. Osmic method described by Cajal. × 420.

FIG. 6.—Dorsal root, diet contained vitamin A oil. Normal. Osmic method described by Cajal. × 420.

Photomicrographs illustrating ventral and dorsal roots of rabbits with and without carotene and vitamin A.

To illustrate paper by Edward Mellanby.

PLATE VII.

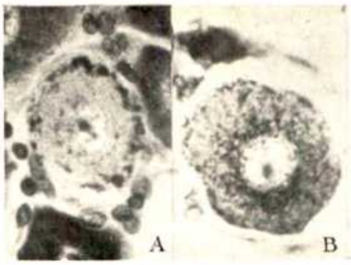


FIG. 1.

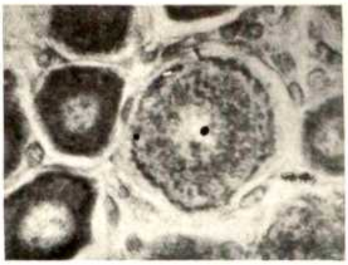


FIG. 2.

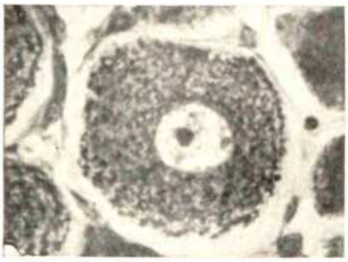


FIG. 3.

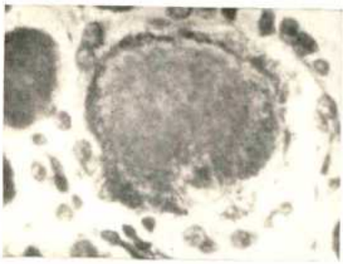


FIG. 4.

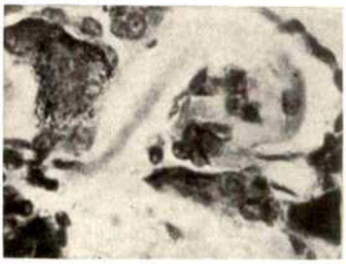


FIG. 5.

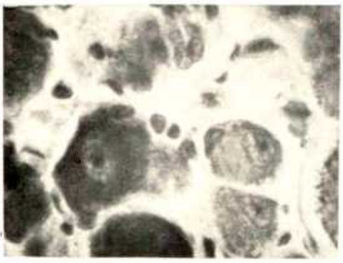


FIG. 6.

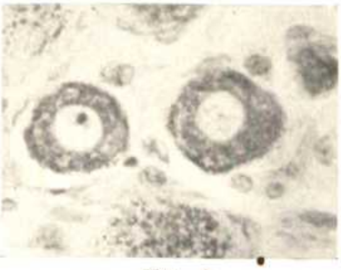


FIG. 7.

FIG. 1.—(*a*) Dorsal root ganglia × 750, large cell showing large granules around outer edge and rest of cell clear. (*b*) Dorsal root ganglia × 750, large cell showing concentration of granules around nucleus.

FIG. 2.—Dorsal root ganglia × 750, large cell showing large granules around outer edge, medium granules throughout.

FIG. 3.—Dorsal root ganglia × 750, large cell. Normal.

FIG. 4.—Dorsal root ganglia × 750, large cell with eccentric nucleus and concentration of granules around outer edge.

FIG. 5.—Dorsal root ganglia × 750, corroded cell of Cajal.

FIG. 6.—Dorsal root ganglia × 750, small cells showing eccentric nuclei.

FIG. 7.—Dorsal root ganglia × 750, small cells. Normal.

Photomicrographs illustrating dorsal root ganglia in rabbits with (figs. 3 and 7) and without carotene and vitamin A (figs. 1, 2, 4, 5 and 6).

To illustrate paper by Edward Mellanby.

PLATE VIII.

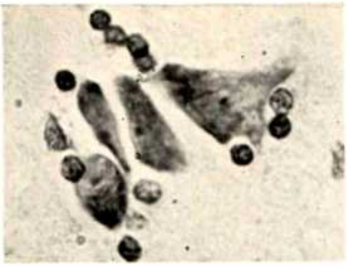


FIG. 1.

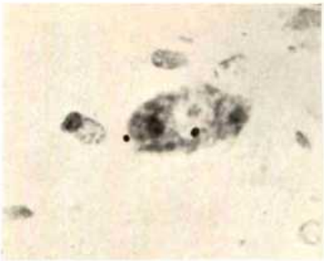


FIG. 2.

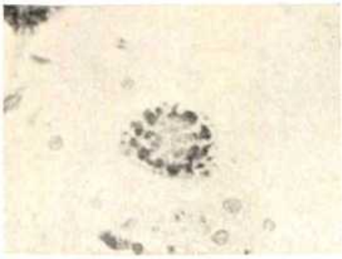


FIG. 3.

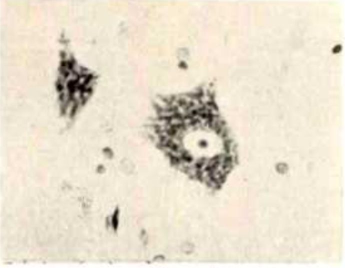


FIG. 4.

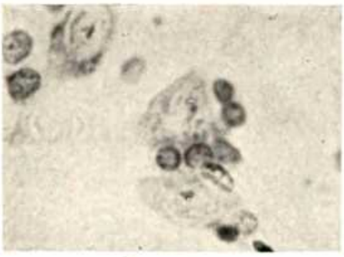


FIG. 5.

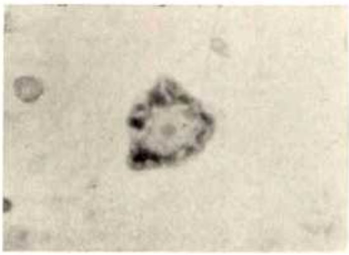


FIG. 6.

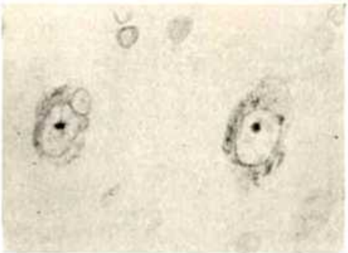


FIG. 7.

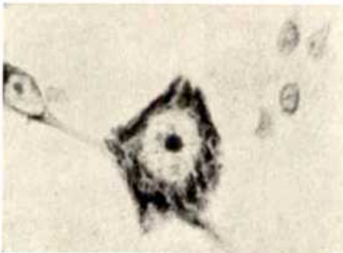


FIG. 8.

FIG. 1.—Clarke's column cells × 750, diet deficient in carotene and vitamin A. Eccentric nuclei, loss of granules and neuronophagia.

FIG. 2.—Clarke's column cells × 750, diet contained cabbage. Probably normal.

FIG. 3.—Ventral horn cells × 420, diet deficient in carotene and vitamin A. Clumping of granules.

FIG. 4.—Ventral horn cells × 420, diet contained yellow maize. Normal.

FIG. 5.—Cells of lateral reticular nucleus × 750, diet deficient in carotene and vitamin A. Loss of granules. Neuronophagia.

FIG. 6.—Cells of lateral reticular nucleus × 750, diet contained carotene. Probably normal.

FIG. 7.—Cells of mesial vestibular nucleus × 750, diet deficient in carotene and vitamin A. Loss of granules. Neuronophagia.

FIG. 8.—Cells of mesial vestibular nucleus × 750, diet contained yellow maize. Normal.

Photomicrographs illustrating cells in the central nervous system of rabbits with and without carotene and vitamin A.

To illustrate paper by Edward Mellanby.

PLATE IX.

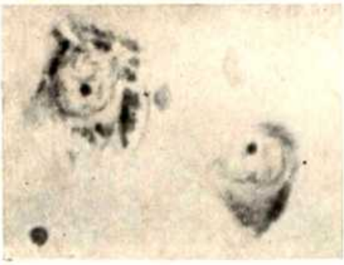


FIG. 1.

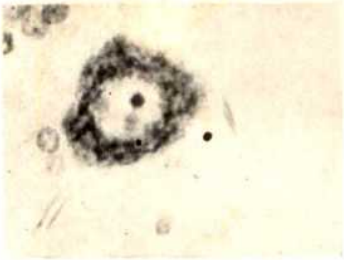


FIG. 2.

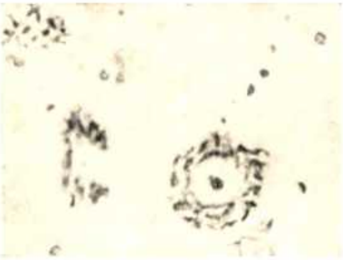


FIG. 3.

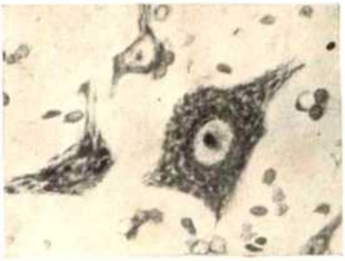


FIG. 4.

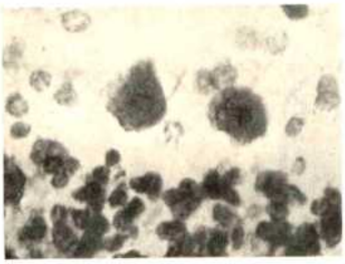


FIG. 5.

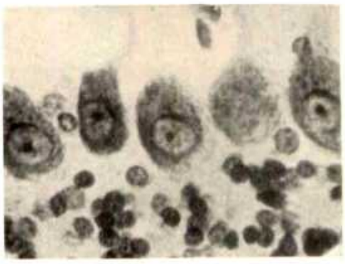


FIG. 6.

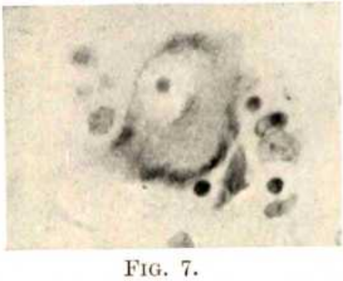


FIG. 7.

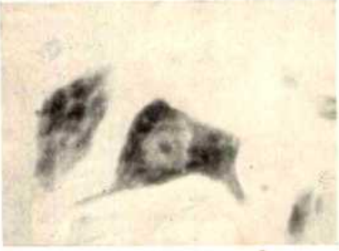


FIG. 8.

FIG. 1.—Cells of oculomotor nucleus × 750, diet deficient in carotene and vitamin A. Chromolysis and eccentric nuclei.

FIG. 2.—Cell of oculomotor nucleus × 750, diet contained carrot. Probably normal.

FIG. 3.—Cells of red nucleus × 420, diet deficient in carotene and vitamin A. Clumping of granules.

FIG. 4.—Cells of red nucleus × 420, diet contained vitamin A oil. Normal.

FIG. 5.—Purkinje cells × 750, diet deficient in carotene and vitamin A. Indefinite granules, loss of demilune and nucleus.

FIG. 6.—Purkinje cells × 750, diet contained cabbage. Normal.

FIG. 7.—Cell of medial accessory olivary nucleus × 750, diet deficient in carotene and vitamin A. Chromolysis and eccentric nuclei.

FIG. 8.—Cell of medial accessory olivary nucleus × 750, diet contained pure carotene. Normal.

Photomicrographs illustrating cells of the mid-brain and cerebellum of rabbits with and without carotene and vitamin A.

To illustrate paper by Edward Mellanby.

peripheral systems of animals receiving the carotene-deficient diet described. The groups of nerve-cells examined include those of the dorsal root and the Gasserian ganglia of the peripheral system, and the cells of Clarke's column, the Purkinje cells, those of the vestibular nucleus and many others in the central nervous system. In this case also, especially in the spinal cord, it is the afferent side which suffers most. In the mid-brain, however, the red nucleus and the dentate nucleus, and sometimes the 3rd nucleus, occasionally show some abnormalities.

I wish to express my indebtedness to my technical assistant, Mr. R. C. Stewart, for the great help he has given in this investigation, especially by improving histological methods so as to allow a large mass of material to be examined. The expenses of the work were paid by the Medical Research Council, to whom my thanks are due.

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THE EFFECTS OF LESIONS OF THE DORSAL SPINO-CEREBELLAR TRACT AND CORPUS RESTIFORME IN THE *MACACUS RHESUS* MONKEY.

BY A. FERRARO, M.D., AND S. E. BARRERA, M.D.

From the Department of Neuropathology, New York State Psychiatric Institute and Hospital, New York.

I.—Introduction.

Studies in comparative anatomy, physiology and clinical pathology have all indicated that the cerebellum as a whole tends to exert some influence which is necessary for proper co-ordination in movement. We are still at a loss for an explanation of the exact mechanisms involved. In its adult mammalian form the cerebellum is a very complex structure, including numerous afferent pathways by which influences of various types are brought to the centrally organized co-ordinated mechanisms in the cerebellum, and efferent pathways over which cerebellar influences are transmitted to reach ultimately the body musculature. For a systematic understanding of the functional organization of the cerebellum it is necessary to know not only the anatomical relationships which lay down the possibilities of physiological responses, but also the functional significance of each of the various afferent and efferent components entering into the cerebellar mechanism.

Experimental physiology has taught us a great deal concerning cerebellar function and would yield still more valuable information if experimental lesions were followed both by careful physiological observations and by careful anatomical control. The lesions should be small enough to be confined to one component, or to one combination of components, so that their effects might be systematically studied. Experiments on higher animals, as the monkey or higher primates, would be advisable. This has not been done except in a few cases. The brain of the monkey offers a cerebellum comparable to that of man, and as in this animal there are more complex types of motility of the limbs than most lower forms it is most suitable for investigations of cerebellar dysfunction.

Our aim has been to study systematically the effects of carefully controlled lesions of each of the components of the cerebellum, and it has seemed that the point of departure would be the observation of the effects of depriving the cerebellum of its various afferent components. We have therefore taken the inferior cerebellar peduncle as a starting point, since it contains afferent components from both the spinal cord and the medulla. This paper will deal with the effects of lesions of the dorsal spino-cerebellar tract in the upper cord, and of the restiform body at various levels in the medulla oblongata where it contains in addition components from the dorsal column nuclei, from the olives and from the nucleus lateralis medullæ.

II.—REVIEW OF LITERATURE.

Nowhere has the literature on the function of one structure been more complicated and contradictory than that on the inferior cerebellar peduncle. This would seem to be due to the complexity of the peduncle, especially at its high levels, and therefore to variability in effects according to the levêl of section and to the close proximity of vestibular centres. Poor anatomical controls, especially with regard to vestibular complications, have been responsible for much of the controversy on this problem. We have found that the symptoms of section of the restiform body, without involvement of neighbouring vestibular structures, differed considerably from those of lesions which also encroached upon the latter. This has convinced us of the necessity for careful microscopical control of all experimental lesions, especially when the functions of small groups of cells or fibres such as are found in the inferior cerebellar peduncle are studied.

The inferior cerebellar peduncle is usually considered as containing spino-cerebellar, dorsal-column-nuclear-cerebellar, olivo-cerebellar, lateral nucleus-cerebellar, and cranio-nuclear-cerebellar components. The exact position of each of these in different animals is very complicated. The spino-cerebellar tracts are considered as the main pathway to the cerebellum from the cord, and in our first investigation we have studied the effects of lesions of the dorsal spino-cerebellar tract in the upper cervical region. Section of these fibres within the restiform body has thrown considerable light on the result of the associated injury of other components of the peduncle.

Comparative anatomy.—According to Kappers [1], the spino-cerebellar tract in Plagiostomes is partly crossed, but is in the main an uncrossed system. It consists of two parts, a smaller corresponding to the ventral spino-cerebellar tract, and a much larger dorsal tract which joins the olivary fibres and passes to the cerebellum. The fibres end directly in the corpus cerebelli. In the Teleosts there are likewise two systems, but the division between the dorsal and ventral portions is sharper. The dorsal spino-cerebellar tract, according to Herrick [2], is best developed in those forms in which there is a great development of cervical sensibility, as in the Triglides and Lophius. It can be followed as a distinct bundle into the cerebellum with the olivo-cerebellar fibres. In the amphibia the dorsal tract is the smaller of the two spino-cerebellar tracts, and most of its fibres end uncrossed in the cerebellum. In reptiles Kappers found essentially the same condition. In birds the two divisions of the spino-cerebellar system are again prominent. Accompanied by the olivo-cerebellar fibres, the dorsal spino-cerebellar tract enters the posterior region of the cerebellum, in which, according to Shimazono [3] and Friedlander [4], it ends predominantly in the dorso-lateral portion of the cortex. Some of its fibres are supposed to surround and even to end in the medial cerebellar nucleus.

There has been considerable controversy concerning the importance of the spino-cerebellar system in higher forms, but the consensus of opinion [5 to 46] seems to be that the dorsal spino-cerebellar tract arises chiefly from the cells of Clarke's column, that it is essentially related to the trunk and hind-limbs, that it is mainly uncrossed, and that it terminates principally in the vermis of the cerebellum. To the variations in different animal species may be due some of the differences of opinion regarding the origin, course and termination of the dorsal spino-cerebellar tract. Few authors have worked with higher forms such as the monkey, but Tooth, Mott, Grünbaum and MacNalty and Horsley all investigated the spino-cerebellar tracts in this animal. Other authors, including Löwenthal, Auerbach, Kohnstamm, Marburg, van Gehuchten, Bing, MacNalty and Horsley, and Ingvar used dogs. Cats as experimental animals were used by Auerbach, Pellizzi, Patrick, Lewandowsky, MacNalty and Horsley, Ingvar, Beck and Pass.

An interesting observation on the dorsal spino-cerebellar tract was made by Sherrington and Laslett, who by their method of " successive degenerations " showed that the tract was stratified, the outermost or more peripheral fibres coming from the lowest segments of the cord. They regarded this as an example of the law that the longer the fibres the further they lie from the grey matter, as they are displaced peripherally by the accession of subsequently entering fibres.

We cannot consider now all of the anatomical evidence for the participation of the various structures which are usually assumed to send fibres into the inferior cerebellar peduncle. Some of the authors divide this structure into an inner and outer portion. The inner portion contains the fibres connecting the vestibular nuclei and the nuclei of the cerebellar roof. This forms the so-called I.A.K. bundle of Meynert (innere Abteilung des Kleinhirnstiel), and is essentially a vestibulo-cerebello-vestibular pathway. The outer portion of the peduncle contains the cerebellar projection of the restiform body after it has passed the level of the eighth nerve and turned upward into the cerebellum. Failure to distinguish accurately between lesions of these two portions of the inferior peduncle has undoubtedly led to much confusion, especially among the earlier authors.

The physiological observations on lesions of the restiform body and spino-cerebellar tract have, except by two or three authors, been poorly controlled histologically. The earlier authors spoke mainly of the "cerebellar peduncle" and did not confine their observations to the result of section of only the inferior cerebellar peduncle or the restiform body. In fact, they did not even differentiate the many components of the large mass of fibres connecting the medulla and pons with the cerebellum, and spoke of the whole mass of what we now know as the superior, middle and inferior peduncles as a single large peduncle.

Serres [47] and Magendie [48] were apparently the first to experiment on the cerebellar peduncles. In unilateral lesions they found that the most constant symptom was torsion movements of the animals around the longitudinal axis to the side of the injured peduncle. The lesions apparently involved all three peduncles. Other authors, as Longet [49], Lafargue [50], and Lussana [51], always found torsion movements toward the side opposite to that of the lesion. Claude-Bernard [52] observed torsion movements toward the side of the injured peduncle when the lesions were caudal to the exit of the fifth nerve. On the other hand, section of the peduncle anterior to the fifth nerve was accompanied by torsion movements towards the opposite side.

Ferrier [53] and Hitzig [54] confirmed in general the findings of Serres and Magendie. Ferrier explained the contradictory reports of previous authors as due to a simple misunderstanding and dependent on whether one looked at the animal from in front or from behind. However, even after Ferrier's explanation, authors differed widely in their descriptions.

Ferrier and Turner (1894) [55] described in detail the symptoms of section of the various cerebellar peduncles in monkeys. In animals in which the left inferior peduncle was cut there was a curving of the vertebral axis to the left, with flexion of the left limbs and extension of the right. Every attempt at movement produced rolling movements from the right to the left, and the animal held on tightly to any means of support. Slightly later they observed tilting of the chin to the right. The falling and rolling movements persisted until the ninth day, and nystagmoid movements were observed. Histological examination revealed that the nucleus cuneatus was involved to some extent and that the restiform body was destroyed just before it bends into the cerebellum. The authors described a characteristeric attitude after section of the inferior peduncle, consisting of curvature of the vertebral axis with its convexity towards the side of the lesion, adduction and flexion on the side of the lesion, and abduction and extension of the opposite limbs. In the majority of the cases the chin deviated to the opposite side.

Biedl, in 1894 [56], reported one case of section of the restiform body in a cat. He found a typical group of symptoms including rolling movements and disorders of motility in the extremities of the operated side, disturbance of co-ordination in the legs and head, and rolling movements toward the opposite side whenever the animal made any effort to move. The author did not present an anatomical description of this lesion, except to say that the descending trigeminal root was involved.

Mott, in his extensive studies of the afferent tracts in the monkey, gave no description of the behaviour of his animals.

So far as sharply circumscribed lesions of components of the inferior cerebellar peduncle were concerned the first work was done by Marburg and Bing. Marburg (1904) divided the dorsal spino-cerebellar tract in dogs, usually on one side at or above the second cervical segment. Two days after the operation the head movements were normal. The ipsilateral fore-limbs were turned outwards, the hind-limbs were in maximal abduction. The pelvis was rotated to the operated side and the vertebral axis was usually concave towards this side. All of these symptoms, except abduction of the hind-limb, were inconstant. The animal usually supported itself on the healthy side. The posterior limbs were usually more closely approximated to the anterior limbs than in a normal animal. There was no deviation toward the healthy side on walking. The animal showed marked uncertainty on climbing stairs. While sitting still very little abnormal was noted except that some animals occasionally rested with the dorsum of the foot downward, suggesting a loss of sensory reflexes. The animals reacted normally to pin-prick. There was no change in muscle tone or in the tendon reflexes. The animals recovered quickly, and after two weeks it was difficult to tell the side of the operation, though a slight abduction of the ipsilateral hind-leg usually persisted.

After bilateral section the dog usually showed definitely postural defects with outward rotation of the feet, maximal adduction of the fore-limbs and abduction of the hind-limbs. The fore-limbs were often crossed. The involvement was much more marked in the hind-limbs. There was marked lateral swaying resembling that of a drunken animal. The disability was greater in complicated actions as climbing stairs. The animal was unable to raise its leg upward while its fore-paw rested on the upper step. There was always some unilateral "paresis" shown by abnormal postures of the feet which the animal did not correct; this condition was only present in the "paretic" limb, and it always ran parallel to the paresis. Sensation and the tendon reflexes were normal. In all these dogs there was degeneration not only of the dorsal spino-cerebellar tract but also of the descending pyramidal tract. It is therefore difficult to evaluate the rôle played by this pyramidal deficiency.

Bing (1906) published an extensive monograph on the significance of the spino-cerebellar system and reported the findings associated with lesions of it. He attributed most of the disability to special forms of disturbance of regulation of the muscles and to a diminution of muscle tonus. To these were due the abnormal postures and movements which were greater in the pelvis and shoulder-girdle musculature. Thus the so-called "principal movements" of Munk, which are supposed to be related to subcortical activity, were chiefly affected. Bending of the trunk to one side would appear to be due to this type of disturbance. Bing also attributed inability to turn toward one side to loss of general basic movements. He noted that the disturbance in the principal movements was more marked in the posterior extremities than in the anterior. The hypotonia was more pronounced in the muscles of the pelvis and shoulder girdles. In the acute stage the ipsilateral limbs were abducted and were used only very slightly for support, the weight being shifted on to the normal side. There was no stumbling or falling. There was also a failure to correct abnormal postures of the limbs. The pelvis was rotated towards the operated side; the vertebral column was normal. The animals appeared normal in sitting and lying postures. The limbs were more adducted in walking, and at times were even crossed. The hind-leg of the operated side was often placed too far forward. The involved limbs showed slight shakiness and ataxia.

There was usually no deviation to one side on walking, but occasionally the animals walked in circles toward the healthy side and presented a considerable difficulty in turning towards the operated side. There was no spontaneous dorsi-placing of the feet. The ataxia was more marked when the animal was blindfolded and in jumping the animal often fell toward the operated side. Tarsal and carpal tone was essentially normal. Sensation and the deep reflexes were undisturbed likewise. Improvement proceeded rapidly, and by the fourth day the abduction was considerably less, muscle tone was approximately normal, and the animal rarely fell.

After four weeks the only difficulty was in turning towards the operated side in search of food. As the author illustrates his anatomical descriptions only by schematic drawings it is difficult to make out the exact extent of the lesions.

Bing disagreed with some of Marburg's findings particularly as pyramidal lesions had complicated the latter's observations. According to Bing the symptoms were due to involvement of reflex paths resulting in a deficiency of afferent stimuli to the cerebellum, for only afferent pathways were cut in his experiments. The symptoms resembled in part those due to sections of the dorsal roots, and he referred to the similarity of the pseudo-paraplegic state of Munk and Bichel, in which animals subjected to centripetal lesions showed ataxic postures. Bing believed that the dorsal spino-cerebellar tract has a bilateral origin. He could not determine exactly the reflex pathway involved, but suggested it was possibly "peripheral sensory neuron to dorsal spino-cerebellar tract, to vermis, to the tractus cerebello-tegmentalis, to the red nucleus, to the rubrospinal tract, to the peripheral motor neuron." He referred to the remarkable constancy of this neuron chain in the animal series; it has been described even in the Selachians.

Bing found no disturbance of cutaneous sensation but considered it possible that the spino-cerebellar tract subserves deep sensibility, and that lesions of this system may therefore disturb muscle tone. Compensation occurs through the cortical, subcortical and spinal pathways. That the fore-limbs were less involved than the hind-limbs in cervical lesions, he considered possibly due to the greater participation of the psychomotor cortex in movements of the arms or fore-limbs. The more severe affection of the hind-limbs may be explained by the distribution of Clarke's column which extends from the lower portion of the cord to the upper dorsal segments.

Bing and Marburg are the only authors who have described at length isolated lesions of the spino-cerebellar or restiform body systems, but brief descriptions have been given by other authors. For instance, Bruce and Schäfer (1910), in studying spinal degeneration in monkeys, mentioned that no permanent symptoms followed lesions of the dorsal spino-cerebellar tract in the upper part of the cord, and that the animal showed very little abnormality in the acute stage.

Bechterew (1908) [57] has also referred to the effects of lesions of the inferior cerebellar peduncles. In dogs he made lesions either below or above the entrance of the eighth nerve. In the animal in which the left inferior peduncle was cut caudal to the entrance of the eighth nerve the head and trunk were rotated around the long axis of the body toward the side of the lesion, with concomitant deviation of the eyes in a diagonal direction and nystagmus. The animal assumed a forced posture lying on its left side, with the ipsilateral limbs flexed and the contralateral extended. In the animal in which the peduncle was cut above the point of entrance of the eighth nerve, there was also turning of the head and trunk toward the operated side with marked deviation of the eyes and nystagmus. The torsion movements around the long axis persisted. The animal always lay on the ipsilateral side with the contralateral limbs extended. Bechterew believed that the effects of the lesions were the same whether the peduncle was cut above or below the entrance of the eighth nerve. He considered that the involvement of the centripetal paths from the spinal cord and the labyrinths to the cerebellum by way of the inferior peduncle was chiefly responsible for the torsion movements around the long axis of the body.

From this summary of the literature it may be seen that little has been done, especially in higher animals such as the monkey, to correlate controlled anatomical lesions and behaviour of the animal. Most of the investigations on the anatomy of the spino-cerebellar tracts or the various peduncles included practically nothing on the behaviour of the animals, while in most publications in which the symptoms are carefully described the anatomical descriptions are poor. And apart from the work of Mott, Bruce, Ferrier and Turner, there are no observations on monkeys. We therefore felt that there is still an opportunity for systematic investigation to be carried out on carefully controlled experimental lines. We adopted the plan of producing lesions limited as far as possible to each of the components of the inferior cerebellar peduncle. Each experiment has been carefully controlled by anatomical serial sections.

III.—PERSONAL OBSERVATIONS.

Experimental technique.—The operations were all performed on *Macacus rhesus* monkeys. Lesions were made at three levels. In the first the dorsal spino-cerebellar tract was divided in the upper cervical region, usually at about C-4 or C-3. The second level was above the caudal origin of the restiform body at about the lower or middle level of the nucleus cuneatus. The third level was higher in the restiform body, just caudal to the entrance of the eighth nerve.

The spinal lesions were made in a very simple manner. After laminectomy the dura was opened and a dorsal root was mobilized just below its point of entrance. A small superficial lesion was made just lateral to the line of separation of the dorsal columns and lateral columns. Usually this could be accomplished with little bleeding. Most of the lesions were made with a small sharp scalpel or a Darling capsulotomy knife, but in a few cases a small curved cautery was used. The dura was usually not sutured so as to avoid any pressure. Occasionally one dorsal root was cut in order to expose the dorsal spino-cerebellar tract more clearly. To produce lesions in the restiform body a suboccipital approach was made to the cerebellum. After the bone had been removed up to the transverse sinuses the dura was opened exposing the postero-inferior surface of the cerebellum. The vermis and medial portion of the lateral lobe were retracted upwards and it was then possible to see clearly the vestibular eminence, the medulla lateral to this, and the eighth nerve curling around the upper lateral surface of the medulla. The lesions were produced by small sharp hooks. The usual sub-occipital closure was performed without suturing the dura. In all cases the animals usually made remarkably rapid recoveries from the ether anæsthesia. One hour after operation they were usually moving around in the cage and attempting to eat. Careful observations of the general behaviour and of the neurological disturbances were made on all animals three hours and twenty-four hours after the operation, and at the latter period moving pictures were taken. The animals were then observed carefully until the time of sacrifice.

Serial sections were made of all brains. They were studied by Nissl's cell stain, the Weigert myelin-sheath stain, and the Marchi method.

In all twenty-two animals were operated on for this series of observations. We shall present here a typical protocol from each of the characteristic lesions at different levels.

Protocol No. 1, *Cer.* 119.

August 1, 1933. *Operation: Section of left dorsal spino-cerebellar tract at the fourth cervical segment.*—A small superficial lesion was made at the level of entry of the left fourth cervical root. Before making the lesion in the cord the fourth left dorsal root was cut in order to be able to expose clearly the lateral surface of the cord. There was no bleeding or visible swelling of the cord.

Three hours after operation.—While coming out of the anæsthesia, the animal has shown no asymmetry of posture. When recovered from the anæsthesia the most marked symptoms are an apparent left-sided weakness associated with ataxia and falling toward the left. There are slight hypotonia and diminution of the reflexes on the left. The right side appears normal. The grip of the left limbs is strong, contrasting sharply with its absence in lesions of the dorsal columns at the same level. There is a left-sided diminution in the placing and hopping reflexes. The ataxia, falling and weakness manifest themselves especially when the animal tries to walk, climb or reach for food. In sitting still there may be at times an increased abduction in the left hind-limb, but no abnormality of posture in the left fore-limb. In walking the left limbs show a dysmetria with occasional excessive lifting or falling and unsteadiness, without, however, any definite dragging of the limbs such as occurs when the pyramidal tract is involved. The animal falls occasionally to the left. When climbing the animal uses both sides of the body fairly well, but the left limbs show a slight lack of steadiness. All the fingers are employed and the grip is firm and secure. The left deep reflexes are diminished as compared with the right. The muscle tone on the left, as tested by resistance to passive movements, is also reduced. The responses to touch, pin-prick, deep pressure and change in position of the limbs seem normal on both sides of the body. There is no evidence of involvement of any of the cranial nerves. The deficiencies at this time were definitely much less disabling than those due to lesions of the dorsal columns. The disability manifests itself chiefly as a sort of dysmetria. This is shown by the occasional missing of an object for which the animal reaches. There is, however, no intention tremor.

September 1, 1933: *Twenty-four hours after operation.*—The general condition of the animal is excellent. There is little abnormal except slight weakness, hypotonia, inco-ordination of movement and diminution of the reflexes in the left limbs, but even these symptoms do not appear to be as marked as they were. The animal no longer falls towards the left, except occasionally when it jumps or runs very fast, then it may stumble slightly towards the left. The symptoms are as marked in the fore-limbs as in the hind-limbs. Vestibular testing reveals normal responses on both sides. The labyrinthine reflexes are undisturbed. The placing and hopping reflexes on the left have recovered to some extent.

September 11, 1933: *Eleven days after operation.*—At this stage it would be difficult to distinguish the animal from a normal monkey, but there are still slight disabilities on the left, such as a tendency to abduction of the left limbs and a slight lack of elasticity in them on landing from a jump. The deep reflexes are also slightly less active on the left. The animal no longer falls to one side and the sensory responses appear normal. The grip is strong and there is no longer any dysmetria.

The animal was killed on this day for study of its nervous system by Marchi's method. The lesion lay directly in front of the fourth dorsal cervical root which had been divided in the operation.

Anatomical Study.

Microscopically the lesion appeared to be confined to the region of the left dorsal spino-cerebellar tract at the level of the fourth cervical segment. The left fourth cervical dorsal root had been cut and its degeneration could be clearly followed into the dorsal columns and upward to the nucleus cuneatus and the nucleus of Clarke-Monakow (nucleus cuneatus externus). Sections of the cord below the lesion revealed no degeneration in the left pyramidal tract.

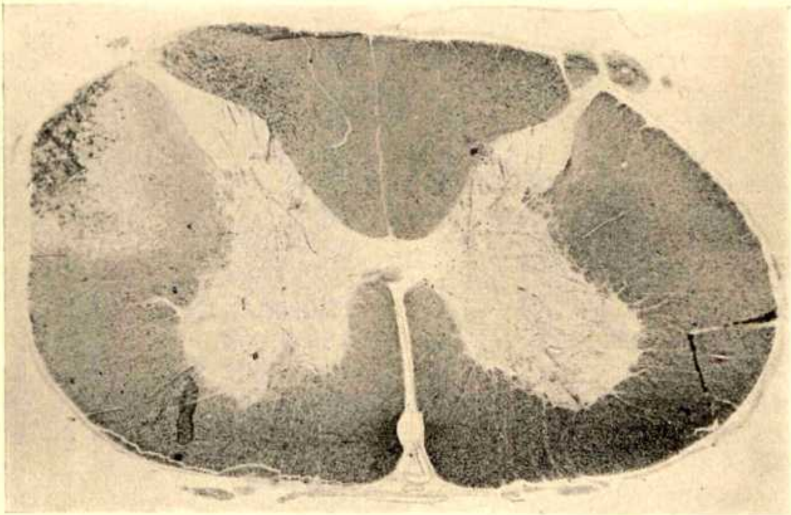

FIG. 1.—Section of the cervical spinal cord at the level of the maximum extent of the lesion, showing the slight paling in the region of the pyramidal tract, which, however, has not produced descending degeneration. The incoming degenerated fourth cervical root, which was cut in the operation, can be clearly seen. Marchi preparation.

Fig. 1 shows a section of the cord at the level of the lesion which is confined to the region of the dorsal spino-cerebellar tract, but there is slight rarefaction in the region of the pyramidal tract. The degenerating fourth cervical root can be seen entering the dorsal column area.

Fig. 2 shows the degenerating fibres just before they pass around the tubercle of Rolando to enter the restiform body. The degenerating fibres from the sectioned fourth cervical root can be seen in the funiculus cuneatus. At higher levels the degeneration can be easily followed in the restiform body, in which the fibres take up a lateral but fairly diffuse position, in perhaps the lateral two-thirds of the restiform body. The medial third is occupied by the entering olivary and dorsal column nuclear fibres, particularly fibres from the nucleus cuneatus externus (Clarke-Monakow). The degeneration can be followed cephalad well up into the lateral portion of the inferior cerebellar peduncle and into the vermis. The exact termination of the tract has not been determined.

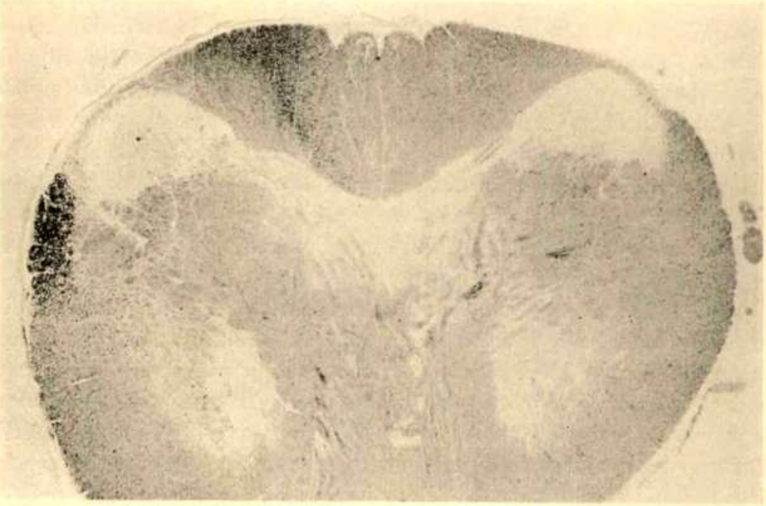

FIG. 2.—Section of the lower medulla at the level of the pyramidal decussation, showing the large group of degenerated fibres of the left dorso-spinocerebellar tract just before they pass around the tubercle of Rolando to form the restiform body. The degenerated fibres of the cervical root in the dorsal columns can be seen on their way to the nucleus of Burdach and the nucleus of Clarke-Monakow. Marchi preparation.

Protocol No. 2, *Cer.* 23.

July 14, 1932. *Operation: Lesion of the right restiform body.*—The floor of the fourth ventricle was exposed by upward retraction of the vermis. At a point where the restiform body runs laterally and at a level of about the middle third of the nucleus cuneatus an incision was made through the restiform body by a fine hook. At the end of the operation the animal was in fine condition. No spontaneous nystagmus was observed.

Three hours after operation.—With the animal well out of anæsthesia the principal manifestation is a weakness in the right limbs and a tendency to fall towards the right side. When the animal attempts to walk its right limbs either slip away on the floor, or crumble and the animal falls towards the right. No involvement of the cranial nerves is observed. The pupils are equal and react well to light. The extra-ocular movements appear normal. The sensory fifth and the biting muscles appear unaffected. There is no facial paralysis and the animal apparently hears well in both ears. No abnormality is noticeable in the position of the head. The chief symptom is an apparent weakness of the right limbs. The tone of the right limbs is much diminished as compared with the normal left limbs. The grip of the limbs is, however, good. The left side of the body appears absolutely normal. When the animal is suspended by the tail with the head downward and the eyes open a normal symmetrical dorsiflexed position of the head is observed. The right limbs are slightly more flexed than the left, which are in the normal semi-flexed position. When the animal is held in the right or left lateral positions with eyes open, positions of the head are normal. The falling reaction is normal. The animal jumps in a straight line, but it lands very heavily on the right side. There are occasionally fine jerky tremors in the right limbs and some evidence of dysmetria in the right fore-limb, for when the animal reaches for a peanut it is apt to miss and fall short of the object at first, but it gradually creeps up so as to grasp it. The deep reflexes on the right side appear slightly diminished. Sensory examinations show no gross disturbance. In this acute stage the symptoms are similar in type but more definite than those due to a lesion of one dorsal spino-cerebellar tract.

July 15, 1932 : *Twenty-four hours after operation.*—The general condition of the animal is essentially the same as at the three-hours' stage, but it no longer falls toward the right side. This now occurs only when the animal attempts to run fast or make a sudden turn, when there may be slight slipping out or giving way of the right limbs. Otherwise the animal gets about fairly well. A slight fine tremor and some dysmetria are still present in the right limbs. The grasp is well maintained. Rotation and caloric tests give normal nystagmus responses in both directions and on both sides. The postural, falling, and righting reflexes are normal.

July 16, 1932 : *Forty-eight hours after operation.*—The general condition of the animal is unchanged, and it seems to be improving rapidly. It runs pretty well with a slight tendency to ataxia and some hypotonia of the right limbs ; when it jumps there is a tendency to land rather more heavily on the right side, and occasionally these limbs slip out. No rotation of the head.

July 21, 1932: *One week after operation.*—The animal now runs pretty well. Save for slight weakness, a tendency to abduction of the right fore-limb, weakness or lack of spring as manifested by heavy landing in jumping and occasionally stumbling when it runs fast, little can be seen which is definitely pathological on either side. There is no evidence of any definite paresis. The reflexes and tone of the right limbs now appear to be normal. Rotation and caloric stimulation give normal responses on both sides. The postural, falling and righting reflexes again give normal responses.

July 28, 1932 : *Two weeks after operation.*—Condition essentially the same as at the one-week stage.

August 14, 1932: *One month after operation.*—The general condition is excellent. There are practically no abnormalities except, perhaps, slight weakness of the right side which is seen only when the animal jumps from a high place. There is a slight tendency when the animal jumps to fling the right limbs slightly higher than the left and to stumble very slightly when it lands, but even this is not definite.

September 14, 1932 : *Two months after operation.*—The condition is essentially the same as at the one-month stage.

October 14, 1932 : *Three months after operation.*—The general condition of the animal is excellent. It now jumps as a normal animal. Little can be seen that might be definitely interpreted as abnormal.

Anatomical Study.

The lesion is confined to the right side and is at the level of the junction of the lower and middle thirds of the right nucleus cuneatus. It involves the brain-stem near the dorsolateral border of the nucleus cuneatus, and passes downward and laterally to just below the inferior border of the restiform body. Fig. 3 shows the lesion at its greatest extent.

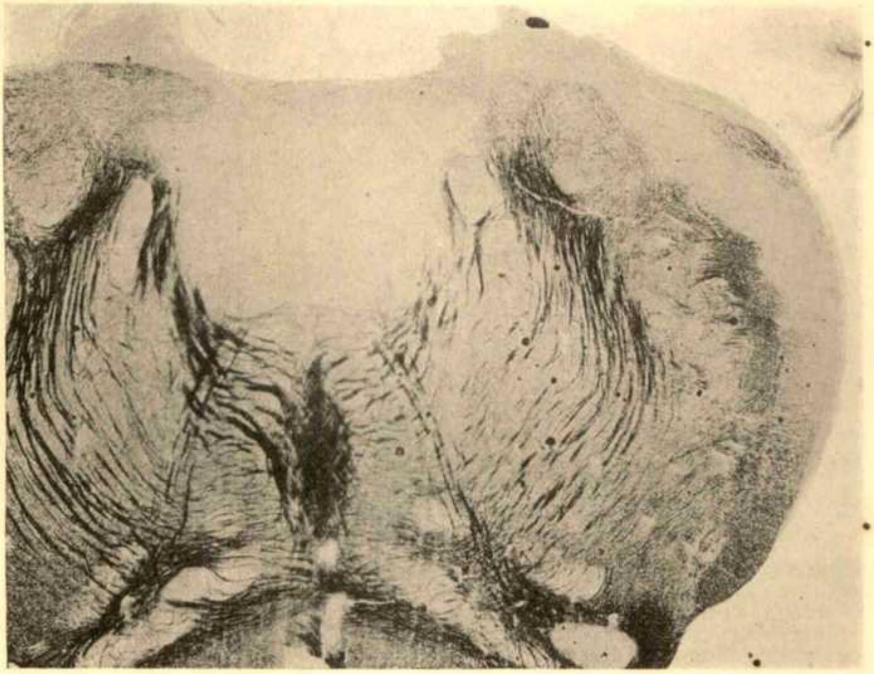

FIG. 3.—Section of the medulla at the level of the maximum extent of the lesion of the right restiform body, showing the direct involvement of the restiform body on the right. The nuclei of Goll and Burdach are not involved to any great extent in the lesion. The few peripheral fibres which are apparently spared at this level, are included in the lesion a section or two higher. Weigert preparation.

The structures involved are the most dorsolateral tip of the nucleus cuneatus, the restiform body, the descending root of the fifth nerve and part of the nucleus of its descending root. Below the lesion in the first or second cervical segments a degeneration is clearly seen in the right descending root of the trigeminus. At the level of the lesion, where the internal arcuate fibres are being formed, there is a slight diminution in these fibres on the right side as compared with the normal left side. The right nucleus cuneatus externus (Clarke-Monakow) is involved in the lesion. At higher levels there is a marked degeneration in the right corpus restiforme, especially in its lateral two-thirds (fig. 4). Still higher the medial border of the corpus restiforme retains a considerable number of relatively normal fibres; these come from the olive. At the level of the trapezoid decussation there is slight paling of the middle portion of the left lemniscus, due undoubtedly to involvement of a few of the fibres from the right nucleus of Burdach. The degeneration in the restiform body can be followed upwards to the vermis. The lesion therefore involved all the fibres of the spino-cerebellar tract, a majority of the fibres from the ipsilateral nucleus of Clarke-Monakow (external cuneate nucleus) and probably some, if not most, of the fibres from the ipsilateral nucleus lateralis medullæ. The extent of the lesion accounts for the greater severity of the clinical manifestations in this case as compared with those of the previous case in which the fibres of the dorsal spino-cerebellar tract only were involved.

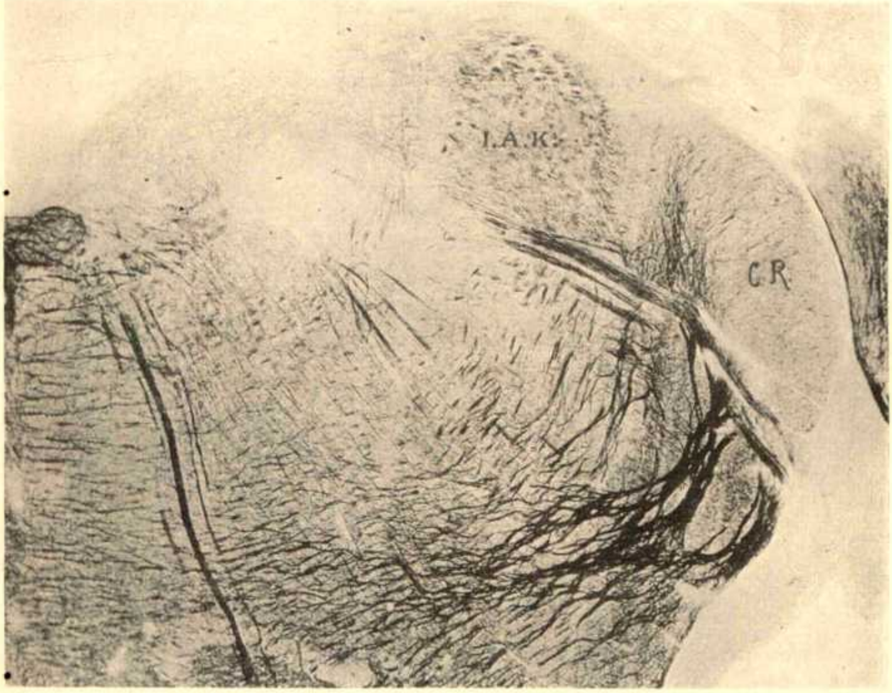

FIG. 4.—Section of the medulla at a higher level than that of fig. 3, at the zone of entrance of the eighth nerve. The restiform body on the right is seen to be degenerated and the incoming olivary fibres are seen to be adding themselves to the restiform body on the medial aspect. There is no evidence of degeneration involving the I.A.K. bundle. Weigert preparation C.R. = corpus restiforme.

Protocol No. 3, *Cer.* 142.

Operation, January 2, 1934: *Section of the right restiform body just below its passage under the eighth nerve.*—The cerebellum was retracted and a small superficial lesion was made in the right restiform body just before it disappeared under the eighth nerve. Very little bleeding occurred.

Three hours after operation.—While the animal was coming out of anæsthesia there was no asymmetry of posture. Whenever the animal attempted to stand, however, it fell to the right side. There has been no spontaneous nystagmus. When the animal had fully recovered from the anæsthetic the symptoms closely resembled those seen in Protocol No. 2, where the lesion of the right restiform body was at a lower level. In the present case, however, the symptoms appear to be more marked and there is a greater tendency to fall to the right. When it attempts to stand it falls over towards the right, perhaps two out of three times. The other disturbances include some ipsilateral hypotonia, depression of reflexes, ataxia, dysmetria and diminution of the placing and hopping reflexes. The animal grasps objects spontaneously in a perfectly normal manner, except for the dysmetria. There are no tremors at rest, no intention tremor, no spontaneous shaking movements and no spontaneous nystagmus. The vestibular reflexes are normal. Sensation, so far as can be determined, is also normal. There are no signs such as rolling movements, asymmetry or nystagmus to indicate the probability of any vestibular complication. When the animal sits it presents abducted postures of the right limbs. It uses the right limbs in reaching for food and grasps a stick or the cage apparently normally.

January 3, 1934: *Twenty-four hours after operation.*—The main symptoms are identical with those found at the three-hours' stage, but the animal does not fall so often to the right side. When it jumps it lands heavily on the right limbs, which tend to sprawl out. This is slightly more pronounced than in animal No. 2. There is no tendency toward rotation of the trunk while it is in the air. When swimming its attitude is symmetrical, and apparently it has normal control over its limbs. Tests reveal no evidence of involvement of the vestibular system, normal responses being obtained from both sides.

January 4, 1934: *Forty-eight hours after operation.*—The condition is essentially the same, the main difference is that the animal can jump somewhat better and avoid falling more easily. No new symptoms have appeared and the stability of the animal seems improved.

January 9, 1934: *One week after operation.*—During the past week the animal has improved considerably. It rarely falls now and only when it makes a sudden movement towards the right side. Muscle tone is still somewhat diminished in the right limbs, and the knee-jerk is still depressed on this side. There has been no evidence of any vestibular complication. The limbs are used well spontaneously, but the animal occasionally misses objects. There has been no asymmetry in posture and no shaking or forced movements of any type. It jumps fairly well and manifests some lack of strength and springiness in the right limbs only when it lands from a long or high jump.

January 14, 1934 : *Twelve days after operation.*—During the past three or four days the animal has improved considerably. It now runs very well, using both sides of the body normally. There is still no evidence of any vestibular complication, but the tone of the muscles and the reflexes are diminished on the right, and there are indications of lack of strength and of spring on this side in jumping.

It was killed on this date and studied with the Marchi method to determine the extent of the lesion.

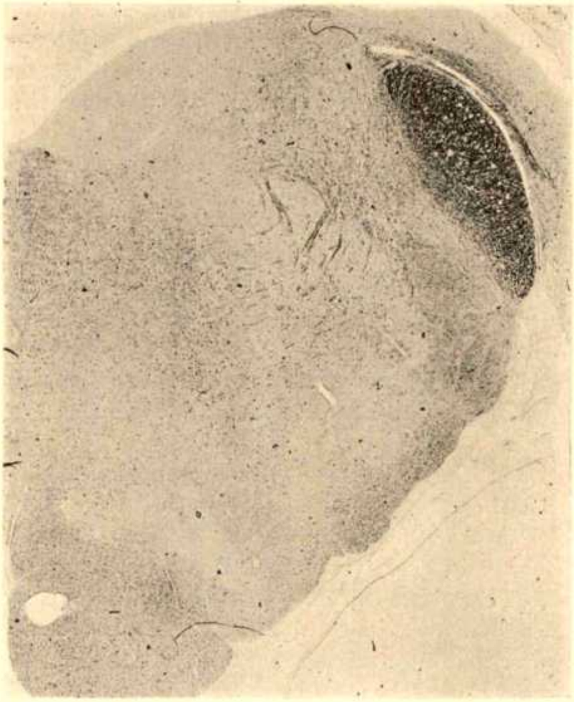

FIG. 5.—Section of the medulla at the zone of entrance of the eighth nerve. The marked degeneration of the right restiform body can be seen. The I.A.K. bundle shows no degeneration. Marchi preparation.

Anatomical Study.

The Marchi preparations are extraordinarily clear. The lesion, which can be clearly delineated, includes the right restiform body in its entire extent at a level about 1 to 2 mm. caudal to the entrance of the eighth nerve. The lesion does not involve the area of the I.A.K. bundle, but is sharply limited to the restiform body itself. In sections below the lesion there is no degeneration in the descending fifth root. Fig. 5 shows a section of the medulla at the entrance of the eighth nerve. Here there is practically complete degeneration of the right restiform body. It can be seen that there is no involvement of the eighth nerve or of the I.A.K. bundle. Fig. 6 comes from a higher level where the inferior peduncle is bending upwards into the cerebellum. A large group of degenerated fibres from the right restiform body can be seen entering the vermis. The lesion involves all the fibres from the spino-cerebellar tract, those from the ipsilateral nucleus lateralis, those from the ipsilateral external cuneate nucleus and a majority of the fibres from the opposite inferior olive.

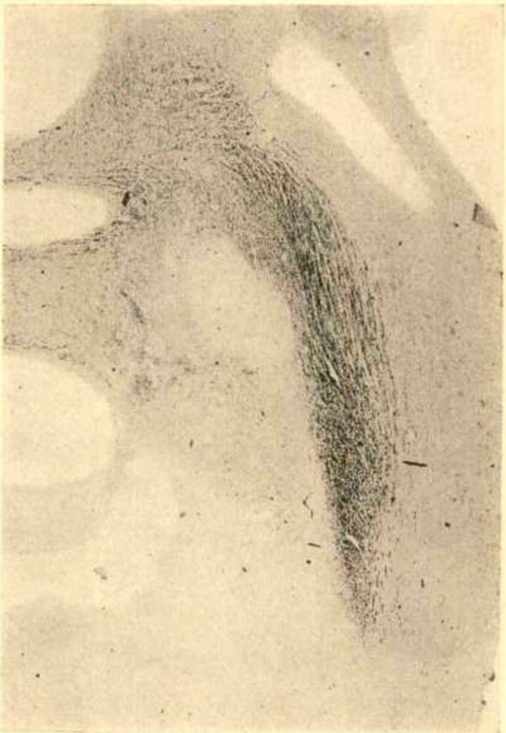

FIG. 6.—Section of the medulla and cerebellum at a level where the inferior peduncle passes dorsally into the cerebellum. The large group of degenerated restiform body fibres can be seen passing dorsally to enter the vermis. Marchi preparation.

Protocol No. 4, *Cer.* 28.

July 14, 1932. *Operation*: *Lesion of both inferior cerebellar peduncles.*—The fourth ventricle was opened with the vermis retracted upwards, the inferior peduncles just lateral, to the vestibular eminence were exposed and a lesion was made with a small hook on each side. Immediately after the lesion, while the animal was still under the anæsthetic, its general condition was good. No peculiarities of posture were observed.

Three hours after operation.—The animal is fully recovered from the anæsthetic; it tends to hug the wall of the cage closely. It occasionally sways from side to side and jerky movements of the limbs sometimes occur. The head is slightly flexed on the chest. When the animal is placed on the floor it tends to extend suddenly all four limbs and to fall flat on the floor banging its head. This may occur suddenly and spasmodically even in an attempt to walk, or the anterior limbs may flex so that the animal suddenly falls on its chest and head. There is no spontaneous nystagmus to indicate any vestibular lesion. All the labyrinthine reflexes appear normal. The deep reflexes are diminished on both sides.

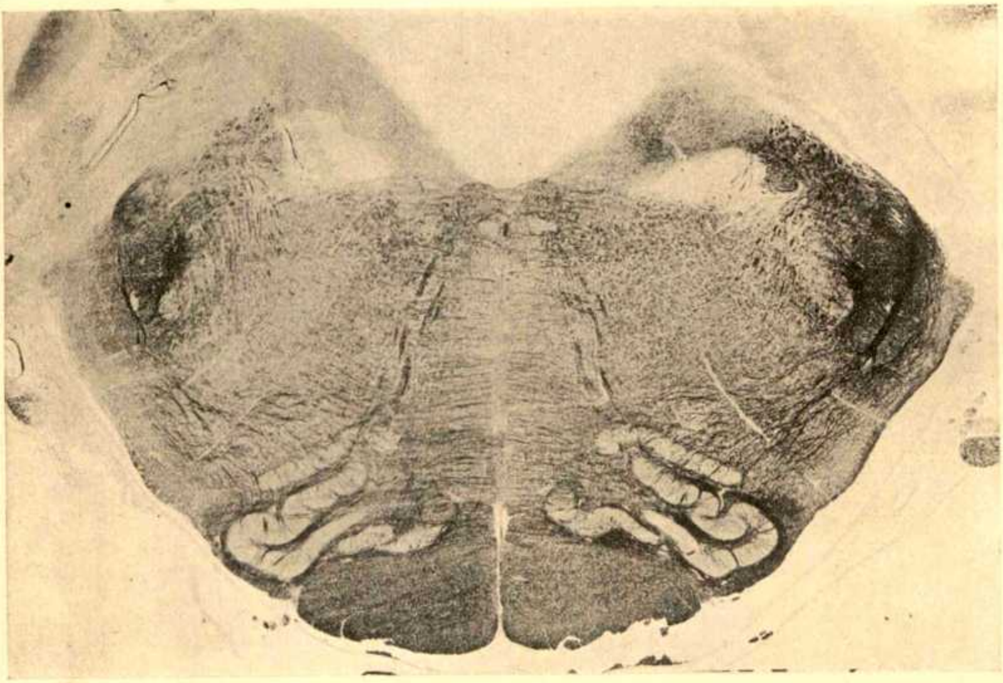

FIG. 7.—Section of the medulla at approximately the maximum point of the bilateral lesion. The lesions are seen to involve both restiform bodies in their entirety. Weigert preparation.

July 15, 1932: *Twenty-four hours after operation.*—The symptoms are unchanged. The animal is still unsteady, walks with a wide base and may fall on its head and chest to the floor. In reaching for food there is definite bilateral ataxia or dysmetria, but no intention tremor. In running across the top of the cage or on the floor it may be unable to stop and plunges headlong into the wall. When the animal is placed on the floor it tends to spring about madly and appears to have no control. It cannot jump toward the cage. When it tries to jump forwards it may leap straight up in the air and land on its back or turn over in all sorts of queer ways, and every once in a while there is a tendency towards forced falling with all limbs extended. The deep reflexes and muscle tone appear diminished throughout. This inability to control the body in motion appears to be due to a lack of control of the limbs rather than to an inability to orient the body or head in space as is found in vestibular animals. When the monkey is held in the air it makes vigorous and mainly successful efforts to right itself. It can swim normally under water. Vestibular tests reveal no disturbances.

July 17, 1932: *Three days after operation.*—The condition of the animal remains the same, but now when it is placed on the floor it does not stumble so wildly. It prefers to lie flat or to walk about slowly.

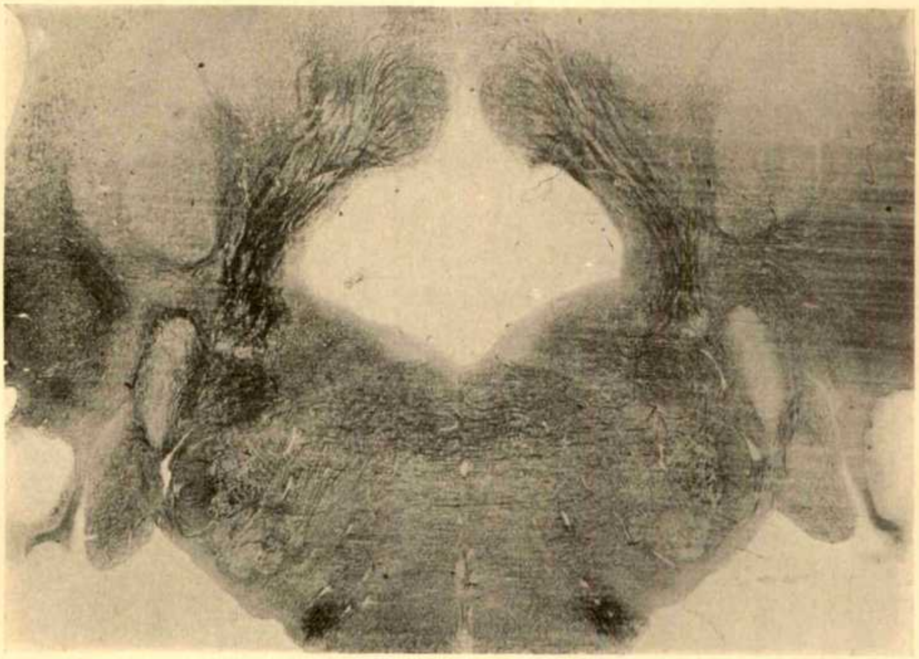

FIG. 8.—Section of the medulla at the level where the restiform bodies bend upward into the cerebellum. The degeneration in both restiform bodies can be clearly seen. The I.A.K. bundles are seen to be well preserved on both sides. Weigert preparation.

July 21, 1932: *One week after operation.*—The condition of the animal is excellent. It appears perfectly at home in the cage, although it manifests a very marked fear reaction. On the floor it still shows a tendency to fall suddenly, and in running there is still undue flexion of the fore-limbs with drooping of the chest and head toward the floor. The ataxia and dysmetria are still present. The deep reflexes and muscle tone now appear about normal throughout.

July 28, 1932: *Two weeks after operation.*—The condition of the animal is essentially the same.

August 3, 1932: *Three weeks after operation.*—It is in much the same state, but it now gets about rapidly on the floor with only slight signs of inco-ordination and lack of control.

August 14, 1932 : *One month after operation.*—There are practically no abnormalities except a tendency when jumping to land heavily on the floor and perhaps to extend all four limbs slightly more than the normal monkey while jumping. The deep reflexes and muscle tone appear normal throughout. The functions of the cranial nerves are unaffected. No tremors or abnormal movements of any type occur in the limbs and there is no ataxia or dysmetria. The falling, position and righting reflexes are normal. Sensory examination and the vestibular tests reveal no disturbances. The animal, however, does not seem to get about very well on the swinging bar and occasionally falls from it. Otherwise it seems sure-footed and climbs quickly and well.

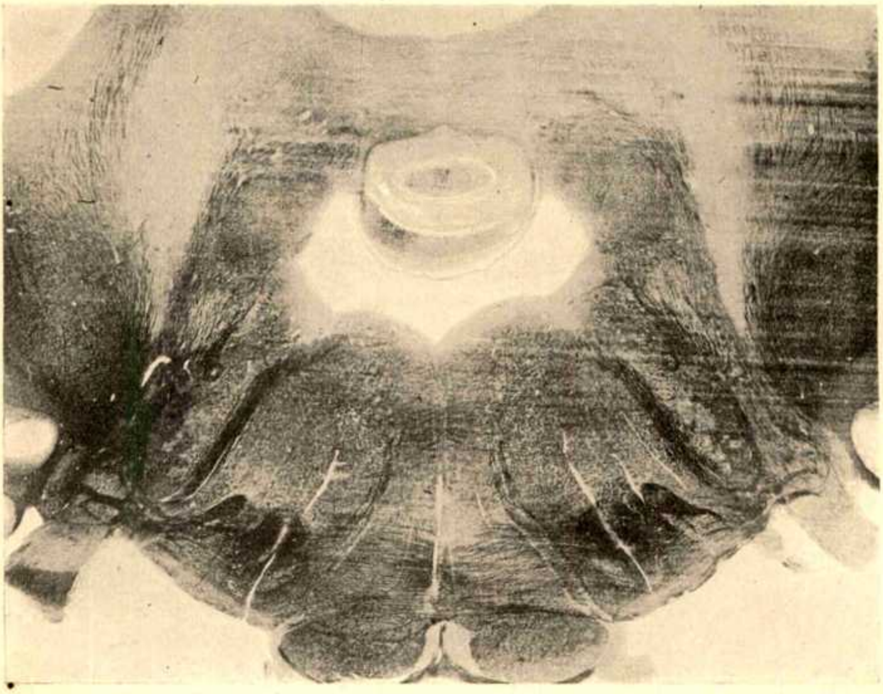

FIG. 9.—Section of the medulla at a higher level than that of fig. 8, showing the fibres from the restiform bodies of both sides radiating dorsally into the vermis. Weigert preparation.

September 14, 1932 : *Two months after operation.*—There is no change ; it is practically a normal monkey.

Anatomical Study.

The lesions involve the restiform bodies near the junctions of the middle and upper thirds of the nuclei cuneati. Weigert preparations of the brain-stem in serial section reveal that the right-sided lesion is slightly higher ; it extends from the angle between the upper outer part of the nuclei cuneati and the restiform body and passes downward and laterally to destroy the restiform body. Fig 7 shows the lesions in their greatest extent. On the left a small part of the inferior portion of the restiform body had apparently escaped, but above the lesion the degeneration appears complete. The uppermost and outer portions of the nuclei cuneati are undoubtedly slightly involved in the cicatrix and there is perhaps slight pallor of the internal arcuate fibres from the nuclei cuneati. At higher levels the lemnisci, however, appear normal. Most of the olivary fibres are involved, but those which enter the restiform body above the lesion escape. The external cuneate nucleus on each side is more damaged. The degenerated restiform bodies can be clearly seen (fig. 8), and the intact fibres of the I.A.K. bundle or vestibulo-cerebellar connections stand out in contrast. Fig. 9 shows the degenerated fibres radiating out to the vermis. The lesions undoubtedly involved the restiform bodies at about their middle. The fibres interrupted by the lesions are those of the spino-cerebellar tracts, those from the nuclei lateralis medulla, those from the external cuneate nucleus and probably the caudal olivo-cerebellar fibres of both sides.

IV.—Discussion.

Section of the dorsal spino-cerebellar tract in our animals produced definite and constant symptoms. These were not complicated by associated damage of the pyramidal tract, for sections of the spinal cords showed no degeneration in this tract. The symptoms were slight ipsilateral weakness, some degree of hypotonia, diminution of the reflexes, slight dysmetria, and in the acute stage a diminution in the hopping and placing reflexes. In the acute stage the animals occasionally fell towards the side of the lesion and the ipsilateral limbs were abducted. These disturbances were transient and had practically disappeared by the end of two or three weeks. Later it was difficult to distinguish one of these animals from a normal monkey.

The same symptoms, but in varying degrees, were found when the lesions involved the restiform body at different levels, provided there were no vestibular complications. Even when the lesion was near the entrance of the eighth nerve we failed to find the rolling movements described by previous authors, as by Biedl in the cat and by Ferrier and Turner in the monkey. These occurred only when the lesion extended deep enough to involve the vestibular apparatus. On the other hand, rolling movements were observed in animals in which we systematically produced lesions of the vestibular system. These will be reported in detail in a subsequent publication.

It is of interest that the symptoms, although similar in type to those produced by section of the dorsal spino-cerebellar tract in the cord, were greater in intensity when the lesions involved the restiform body in the medulla. The severity of the disturbances seems to increase the higher the level at which the lesions injured the restiform body, indicating the involvement of fibres of other sources with similar types of function, for example, the large bundle of fibres from the external cuneate nucleus which enters the outer side of the ipsilateral restiform body. The external cuneate nucleus, which has been variously described as the nucleus of Monakow, the nucleus of Blumenau, the nucleus corporis restiformis, nucleus cuneatus externus, &c., receives fibres by way of the funiculus cuneatus from the cervical and upper dorsal roots, and sends fibres into the ipsilateral restiform body. This nucleus of Clarke-Monakow, as we prefer to call it in honour of Clarke [58] who first decribed it, and Monakow [42], who first recognized its cerebellar connections, undergoes atrophy when the cerebellum is removed or when the inferior peduncle is cut at a high level, indicating that the nucleus sends its fibres into the inferior cerebellar peduncle. In one animal in which we injected alcohol into the caudal half of this nucleus, the symptoms were similar to those of the lesion of the dorsal spino-cerebellar tract. Many authors as Gudden, Monakow, Edinger, Flechsig, Mingazzini, Lewandowsky, Mussen, &c., have stated that each dorsal column nucleus sends fibres into the restiform body, particularly into that of the opposite side, which originate, according to them, from the nuclei gracilis and cuneatus, irrespective of the nucleus of Clarke-Monakow (anterior external arcuate fibres). The posterior external arcuate fibres from the nuclei gracilis and cuneatus reach the homolateral restiform body. And according to Klimoff, Darkschevitch and Freud, Goldstein, &c., crossed and direct fibres from the posterior columns pass directly into the cerebellum. The existence of these fibres is still a matter of doubt.

In addition to these contingents of fibres our work has shown that the nucleus of Clarke-Monakow (external cuneate nucleus) establishes an important connection between the dorsal roots from the upper extremities and neck and the inferior cerebellar peduncle. Section of the restiform body above the level of this nucleus may therefore be expected to produce more intense symptoms than lesions of the dorsal spino-cerebellar tract in the spinal cord.

Another addition to the upper part of the restiform body is the large olivo-cerebellar contingent, arising from the opposite olive. These fibres enter the restiform body on its mesial aspect at the level of entrance of the eighth nerve.

A further group of fibres is received from the so-called nucleus lateralis medullæ. This nucleus undergoes atrophy after lesions of the ipsilateral inferior cerebellar peduncle even at fairly low levels.

It may therefore be expected, in view of the numerous contingents which enter the restiform body as it passes upwards, that the symptoms associated with lesions of it at various levels may vary. The intensity of the disturbances increases as the lesions lie more cephalad, but no new symptoms appear. The tendency to fall to the side of the lesion particularly, increases as the lesion lies higher in the restiform body.

It may be noted that in our descriptions of the animals, most of the symptoms appeared to be explicable on the basis of deficient afferent impulses to the cerebellum from the limbs. There were no symptoms of abnormal activity such as rolling movements, spontaneous tremor at rest (except transitory tremor in the acute stage) intention tremors, or spontaneous nystagmus in pure lesions of the spino-cerebellar tract or restiform body. Such symptoms have been described by almost all previous authors who have experimented on the inferior cerebellar peduncle in the monkey and other animals. There is little doubt that these active symptoms are due to complicating factors such as extension of the lesion beyond the restiform body proper. They occurred in many of our other animals in which the lesions extended into the vestibular nuclei or involved the secondary vestibular connections such as the I.A.K. bundle (juxtarestiform body). In these animals the symptoms differed from those in which the restiform body or dorsal spino-cerebellar tract only were injured, and included rolling movements toward the side of the lesion, spontaneous tremors, abnormal postures of the head, spontaneous nystagmus, &c. As the vestibular nuclei and the secondary vestibular connections lie close to the restiform body, especially in its higher levels, in the absence of serial anatomical controls small but significant lesions which may complicate the symptoms can be missed easily.

An interesting feature of the experiments is the ability of the animals to compensate practically completely the disturbances of cerebellar function due to bilateral lesions of the restiform body. After two or three weeks, even in the presence of bilateral lesions which interrupt all the afferent impulses from the limbs to the cerebellum by way of the restiform body, the animal may jump about, climb and use its limbs practically as well as a normal monkey. The other sources of afferent impulses to the cerebellum are the middle peduncle from higher levels and the vestibular connections between the medullary vestibular nuclei and the nuclei of the cerebellar roof, but none of these are directly related to the limbs. It is of interest that the symptoms are more persistent if, in addition to injury of the restiform bodies, there are lesions of the vestibular apparatus, either of the vestibular nuclei or of the I.A.K. bundle. Then the animal may never, at least within eight or nine months, compensate to any great extent the combined disturbances.

Another point of interest is the comparison between the results of lesions of the dorsal spino-cerebellar tract in the high cervical region with those following unilateral section of the dorsal columns at the same level. The disability due to the latter is much more marked and differs in type too. In the first place lesions of the dorsal columns lead to practically complete loss of spontaneous movements in the limbs; the animal does not grip any object spontaneously and seems incapable of closing its fingers around any object of support, while the animal with a lesion of the dorsal spino-cerebellar tract is perfectly capable of reaching out with the arm or leg of the affected side and of grasping a support accurately and with good strength. Lesions of both the dorsal columns and of the spino-cerebellar tract are associated with diminution in muscle tone as determined by resistance to passive movements, but this is more marked in the presence of lesions of the dorsal column. When the dorsal columns are injured the deep reflexes are active and even appear at times to be over-active, while in lesions of the dorsal spino-cerebellar tract they usually appear slightly decreased. That this is not due to involvement of the pyramidal tract is shown by the fact that similar decrease of the knee-jerks is found when the lesion is made in the restiform body above the level at which the pyramidal fibres could possibly be injured.

Animals with lesions of the restiform body, regardless of the level, are always perfectly capable of grasping objects spontaneously and of using the limbs in practically every type of movement. When the dorsal-column nuclei are injured they lose the ability to perform spontaneous movements with the limbs and are incapable of grasping objects or particles of food, exactly as when the dorsal columns are divided.

In a previous communication on the effects of lesions of the dorsal columns [59] we have shown that when they are injured by lesions in the cervical segments the symptoms are more severe in the fore-limbs than in the hind-limbs. This was attributed to the combination of dorsal column elements and cerebellar elements in the dorsal columns at these levels. The cerebellar elements are those which enter the dorsal columns to pass to the ipsilateral restiform body by way of the external cuneate nucleus (nucleus of Clarke-Monakow). The direct pathway for cerebellar representation from the upper limb has, in contrast to that from the hind-limb, been always obscure. It has been assumed that the dorsal spino-cerebellar tract carries impulses only from the trunk and hind limbs, but in our experimental animals in which only the dorsal spino-cerebellar tract was injured in the cervical region, the ipsilateral fore-leg was affected in the same manner as it was by lesions of the restiform body, and the symptoms in it were just as severe as those in the hind-limb. This indicates that in addition to the dorsal column cerebellar component from the upper limbs there must be another component which reaches the inferior peduncle by way of the dorsal spino-cerebellar tract.

Our present work has not established accurately the origin and terminations, or even the minute anatomy, of the dorsal spino-cerebellar tract, but it shows that after reaching the restiform body the fibres of this tract tend to take a lateral course in the restiform body while the fibres from the various medullary components are added to the mesial portion of the restiform body. At higher levels this position is possibly reversed, inasmuch as the fibres from the olive, for example, may reach the lateral lobes of the cerebellum whereas those of the dorsal spino-cerebellar tract ultimately pass to the vermis. This would necessitate a crossing of these fibres somewhere in the course of the inferior cerebellar peduncle.

V.—CONCLUSIONS.

(1) Section of the dorsal spino-cerebellar tract in *Macacus rhesus* monkeys, unassociated with any pyramidal tract involvement, produces a definite group of symptoms consisting of ipsilateral weakness of the limbs, slight hypotonia, diminution of the reflexes, slight dysmetria and, in the acute stage, a diminution in the hopping and placing reflexes; occasionally, in the acute stage, the animal tends to fall toward the side of the lesion, and the ipsilateral limbs while at rest assume abducted postures.

(2) The disturbances practically disappear by the end of two or three weeks. Later it is difficult to distinguish one of these animals from a normal monkey. Only a slight loss of elasticity in the ipsilateral limbs may persist.

(3) The symptoms associated with section of the restiform body are

the same in type as those which result from section of the dorsal spino-cerebellar tract. The only difference is one of intensity, as the lesions of the restiform body are followed by a more pronounced dysmetria, hypotonia, ipsilateral weakness and diminution of the reflexes.

(4) The symptoms are the same in type regardless of the level at which the restiform body is divided, but their intensity is greater, the higher the lesion is placed. The explanation is that lesions in the upper part of the restiform body involve new contingents of fibres from various structures which join the restiform body to enter the cerebellum (contingent from the nucleus funiculi lateralis, contingent from the nucleus of Clarke-Monakow and contingent from the olives).

(5) We have never observed after section of the restiform body forced postures or movements, such as rotation around the long axis of the animal, or deviation of the head or chin to one or the other side. These phenomena do not, therefore, constitute an integral part of the symptomatology of lesions of the restiform body as previous investigators have stated. They appear only when the vestibular apparatus (vestibular nuclei or I.A.K. bundle) is also injured.

(6) The lesions of the dorsal spino-cerebellar tract in the higher cervical segments of the cord is followed by disturbances in the ipsilateral upper extremity. We therefore assume that part of the cerebellar representation of the upper limbs must be established through the dorsal spino-cerebellar tract. There is also another pathway which connects the posterior columns with the cerebellum by way of the external cuneate nucleus or nucleus of Clarke-Monakow.

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THE MECHANISM OF INTERNAL HYDROCEPHALUS IN SPINA BIFIDA.

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THE frequent association of hydrocephalus with spina bifida has been observed for centuries but no explanation of this association has yet proved generally acceptable. Morgagni (1769) thought that the hydrocephalus was the primary disorder and that the excess of fluid present caused the spinal defect and the bulging sac at the site of this bony deficiency. Both he and subsequent observers had difficulty, however, in accounting for the occurrence of spina bifida without hydrocephalus. In the latter part of the last century the association came to be explained in terms of teratogenesis but without any precise conception of the mechanical factors responsible for the hydrocephalus. At that time little was known, however, of the way in which the cerebrospinal fluid is formed and circulates. The work of Lewis Weed (1914) and of Dandy and Blackfan (1914) has thrown much light on these problems and has led to the recognition of "communicating" and "non-communicating" types of internal hydrocephalus. In the former a dye injected into one or both lateral ventricles can be recaptured within a few minutes from the lumbar subarachnoid space; in the latter this is rendered impossible by the presence of a block which prevents in some part of its course the passage of cerebrospinal fluid from the lateral ventricles to the spinal subarachnoid space.

In this paper a mechanical explanation is offered of the production of communicating hydrocephalus in a series of cases of meningo-myelocele. Further, the examination of a single case of meningocele without hydrocephalus suggests that the same mechanism may sometimes operate also in this type of spina bifida. To determine the factors responsible for hydrocephalus in any given instance it is desirable that the anatomical study should be carried out in the light of a clinical test to discover whether the hydrocephalus is of the communicating or of the non-communicating type. Unfortunately this has been practicable in only a few instances. The study of pathological anatomy alone may, however, give a satisfactory clue to the nature of the hydrocephalus.

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[1] Working for the Medical Research Council.

MENINGO-MYELOCELE.

(1) *Material.*

A series of ten consecutive cases of lumbo-sacral or dorsi-lumbo-sacral meningo-myelocele have been examined. Their principal clinical and anatomical features are presented in the accompanying table. Internal hydrocephalus was present at birth in all except two examples (Cases 4, 6). In two only of the eight cases in which hydrocephalus was present was it demonstrated, by the injection of dye or india ink, to be of the non-communicating type

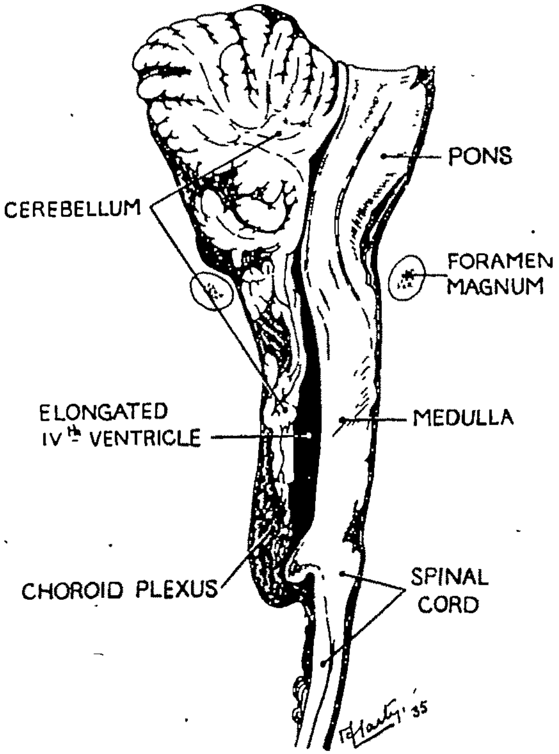

FIG. 1.—Case 10. Median sagittal section through brain-stem to show Arnold-Chiari malformation. Gross elongation of medulla.

(Cases 5, 8). In Case 5 there was atresia of the Sylvian aqueduct and in Case 8 the foramina of Luschka and Majendie were imperforate. A communicating hydrocephalus was present in three examples (Cases 2, 3, 7). In Case 7 this was demonstrated by the injection of india ink into the ventricles. In Case 2 there was an ascending purulent meningitis and it was evident, from the path of the infection, that the hydrocephalus was of the communicating type. In Case 3 a similar conclusion was reached from the anatomical examination. In the three remaining cases (1, 9, 10) the determination of the type of hydrocephalus present was not practicable.

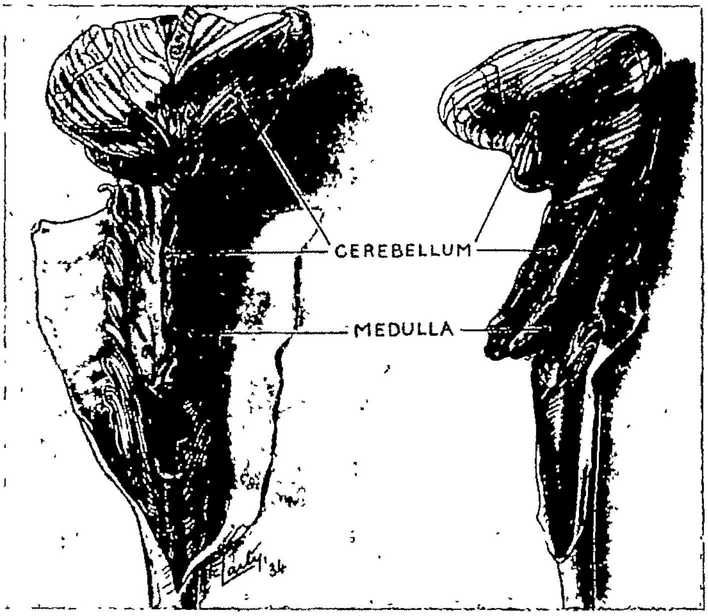

FIG. 2.—Case 8. Dorsal and lateral view of Arnold-Chiari malformation.

In both of the cases (4, 6) in which hydrocephalus was absent the cerebrospinal fluid escaped freely from the body through a fistula in the membrane covering the spinal defect; hence there was no back pressure along the cerebrospinal pathway and no hydrocephalus. In Case 4 the infant survived birth for eleven days and pyocephalus developed as a result of an ascending infection of the cerebrospinal pathway.

(2) *Malformation.*

In all ten examples a remarkable malformation of the hind-brain was observed. In this a tongue of variable length, consisting of cerebellar tissue and the greatly elongated medulla oblongata, protrudes downwards into the spinal canal (figs. 1, 2). It overlaps and compresses the upper segments of the cervical cord, distending the dural theca in this neighbourhood and filling the foramen magnum. The cavity of the fourth ventricle extends caudally into this tongue, lying between the cerebellar and medullary components. The maximum diameter of the ventricle is usually within the vertebral canal at and below the level of the foramen magnum, and here too or at a still lower level are found the choroid plexuses and the foramina with which they are associated. The plexuses are sometimes united into one mass which lies in the middle line in the ventricular cavity (fig. 4). The floor of the ventricle, formed by the elongated medulla oblongata, presents the characteristic markings of the rhomboid fossa, and in the middle line towards its caudal extremity is a minute pore which provides a horizontal communication between the ventricle and the central canal of the ventrally placed spinal cord. The cavity of the ventricle usually extends beyond this pore as a diverticulum into the tip of the tongue-like mass. Cross-sections of the brain-stem show a somewhat complicated pattern according to the number of structures involved. Examples are diagrammatically shown in figs. 3 and 4; these also demonstrate the variations that exist in the relative lengths of the cerebellar and medullary components found in the malformation. These diagrams and the drawing in fig. 2 represent dissected specimens; in the undissected

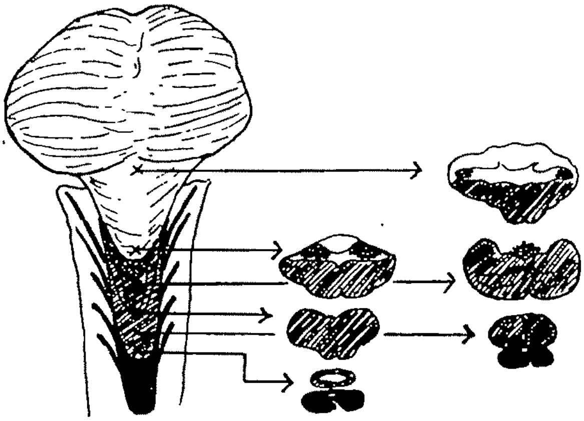

FIG. 3.—Diagram of the malformation in Case 4. Unshaded part = cerebellum; diagonally shaded part = medulla oblongata; black = spinal cord; granular areas = choroid plexus.

specimen the malformation is greatly obscured by the investing leptomeninges which are usually thick, gelatinous and remarkably vascular.

A number of other structural abnormalities are commonly found in association with this malformation. The spinal cord appears abnormally small and the cervical roots always run in a cephalic direction to reach their exits through the dura mater (fig. 2). Their cephalic direction decreases as successive segments are examined until, in the upper thoracic region, they are either horizontally or caudally inclined. Hydromyelia is commonly present in a variable number of consecutive segments in the cervical and thoracic cord. There is a conspicuous hypoplasia of the cerebellum which is usually composed of a small compact mass lacking differentiation into vermis and lateral lobes. The tonsils and flocculi can seldom be identified. The pons as well as the medulla oblongata is elongated and lacks the characteristic ventral protuberance. It is poorly demarcated from the medulla. In addition the cranial nerve roots arising from the pons and medulla are greatly elongated; for example, in Case 6 the sixth roots measured 2·1 cm. to their foramina, the eighth roots 1·7 cm. and the fifth roots 1·3 cm. The

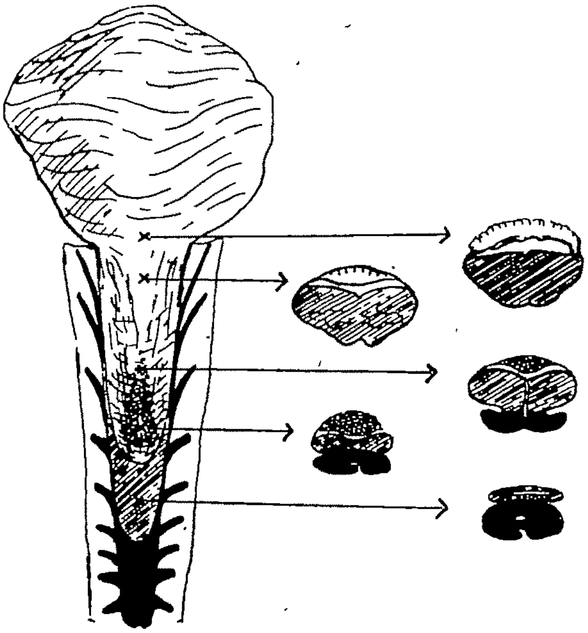
FIG. 4.—Diagram of the malformation in Case 9. Conventions as in fig. 3.

corpora quadrigemina are poorly defined and are sometimes fused into a single conical mass.

This curious maldevelopment was noticed first by Arnold (1894) in a case of spina bifida described as an example of "Myelocyste"; it was more fully described in the following year by Chiari in a series of seven cases of spina bifida, one only of which was more fully particularised as an example of meningo-myelocele. A good description in five cases of meningo-myelocele was published by Solovtzoff (1901), but perhaps the best and fullest account is that of Gredig and Schwalbe in four cases of meningo-myelocele (1907). The last-mentioned authors give a detailed study of the dislocation of nerve-tracts caused by the malformation and it is not proposed, therefore, to describe the microscopic anatomy in the present series. They called this lesion the *Arnold-Chiari malformation* and it is convenient to adopt this name.

(3) *Relation of the Malformation to Hydrocephalus.*

The elongated fourth ventricle extends for a considerable distance below the foramen magnum. It follows that if the foramina of Luschka and Majendie are patent the cerebrospinal fluid escapes into the subarachnoid space within the vertebral canal. The plugging of the upper cervical part of the canal by the Arnold-Chiari malformation is likely to hinder any upward flow of fluid into the subarachnoid channels within the posterior fossa, into which it normally passes on its way to escape through the cranial arachnoid villi. According to the experiments of Dandy and Blackfan (1914) the greater proportion (three-fourths to four-fifths) of cerebrospinal fluid is absorbed from the surface of the brain and from one-fourth to one-fifth only from the spinal canal. Accepting this estimate it follows that occlusion of the foramen magnum in these cases of spina bifida will lead to a damming back of cerebrospinal fluid in the ventricular system and hence to internal hydrocephalus. Certain evidence can be advanced in support of this hypothesis from study of our series of cases.

Experimental evidence.—In Cases 4 and 7 a suspension of india ink was introduced into the lateral ventricles when death was imminent and the distribution of the particles examined at necropsy. On naked eye examination there was a profuse deposit of pigment throughout the ventricular system and in the subarachnoid space of the spinal canal below the level of the Arnold-Chiari malformation. Above this level the leptomeninges in Case 4 appeared to be devoid of pigment, although on microscopic examination a few particles were found within macrophages in the leptomeninges over the mid-brain. In Case 7 a moderate amount was visible at the base of the brain and a very little in the sulci over the cerebral convexities. From this it is inferred that an appreciable though incomplete blockage was present at the foramen magnum in both cases, the degree being greater in Case 4 than in Case 7. Patency of the leptomeningeal spaces over the cerebral convexities was

CASES OF MENINGO-MYELOCELE.

No.	P.M. No.	Sex and Age	Site of spina bifida	Hydrocephalus	Arnold-Chiari malformation	Remarks
1	219.30	M. 8/365	Lumbo-sacral	Congenital; type undetermined	Present	C.N.S. received for investigation after necropsy
2	334.31	F. 4/52	Dorsi-lumbo-sacral	Congenital (communicating)	Present	Ascending meningitis. Type of hydrocephalus inferred from path of infection
3	336.32	M. 2/365	Dorsi-lumbo-sacral	Congenital (communicating)	Present	Type of hydrocephalus inferred from anatomical examination of brain stem
4	463.32	M. 11/365	Lumbo-sacral	Acquired pyocephalus (communicating)	Present	Fistula at spinal defect. Ascending infection followed by pyocephalus. India ink injected into lateral ventricles just before death
5	235.33	F. Still born	Lumbo-sacral	Congenital (non-communicating)	Present	Methylene blue injected into lateral ventricles before necropsy. Atresia of Sylvian aqueduct
6	339.33	F. 2/365	Lumbo-sacral	Absent	Present	Fistula at spinal defect. Methylene blue injected into lateral ventricles before necropsy escaped freely through fistula.
7	395.33	F. 7/365	Lumbo-sacral	Congenital (communicating)	Present	India ink injected into lateral ventricles just before death
8	396.33	F. 7/365	Dorsi-lumbo-sacral	Congenital (non-communicating)	Present	India ink injected into lateral ventricles before death. Imperforate 4th ventricle foramina
9	164.34	M. Still born	Lumbo-sacral	Congenital; type undetermined	Present	Post-mortem softening too advanced to investigate type of hydrocephalus
10	501.34	F. Still born	Dorsi-lumbo-sacral	Congenital; type undetermined	Present	Perforation of brain to facilitate delivery

also demonstrated by the distribution of the particles in Case 7, so that a defect in this respect cannot be advanced as an alternative explanation of the hydrocephalus in this case.

Pathological evidence.—In two instances (Cases 2 and 4) there was an ascending purulent leptomeningitis and pyocephalus following infection of the tissues at the site of the spinal defect. Examination of these specimens, both macroscopically and microscopically, showed a severe purulent infiltration of the spinal meninges up to the level of the Arnold-Chiari malformation, but above this level the inflammatory reaction was mainly confined to the ventricular system where a conspicuous pyocephalus was present. In neither instance was there any macroscopic infiltration of the basal meninges, but microscopically a slight degree of infiltration was found about the mid-brain in both. These findings suggest some degree of obstruction at the foramen magnum to the upward passage of organisms within the leptomeningeal spaces.

Other evidence.—Lastly, certain clinical observations are relevant to this discussion. It has for long been known that operative removal of the sac in spina bifida is frequently followed by hydrocephalus when this was not present before the operation. Now it has been shown by Penfield and Cone (1932) that the soft tissues of the sac absorb cerebrospinal fluid, and these authors claim that hydrocephalus can be avoided if the walls of the sac are conserved. They explain this result by postulating that the normal mechanism for the absorption of the fluid is imperfectly developed in these subjects (private communication). But in terms of the theory advanced in this paper the development of hydrocephalus after operative removal of the sac can be simply explained as a decompensatory effect. It is not unreasonable to suppose that the extra absorbing apparatus provided by the sac may be just sufficient to balance the degree of obstruction at the foramen magnum in instances where such obstruction is not severe. If this is true then operative removal of the sac will disturb this balance and will be followed by the development of internal hydrocephalus.

MENINGOCELE.

The material so far described has been limited to meningo-myelocele. Hydrocephalus has also been observed in many cases of meningocele; in some of these it has been congenital and in others it has followed operation. Inasmuch as these are more favourable cases for surgical treatment than examples of meningo-myelocele, it is of practical importance to discover whether they also are liable to present any malformations of the brain stem. From this point of view it is unfortunate that no comparable series of cases has been available for anatomical study. One example only of meningocele has come to necropsy within the period of this study. This will be fully described because it possesses features that, in our view, bring this class of case into line with those already described.

Clinical. Reg. No. 21882. 1934. Surgical. A female infant was admitted when three days old to the London Hospital on July 16, 1934, under the care of one of us (C.D.) with a translucent cystic meningocele, about 6 cm. diameter, over the sacrum. There was no hydrocephalus and no further demonstrable abnormality in the nervous system. Operative interference could not be delayed on account of threatened rupture of the sac. On August 7 the greater part of the sac was removed because it was too tenuous and poorly nourished to be preserved. What remained of the underlying meninges was puckered up, and the muscles on either side were freed and approximated in the middle line. The skin when sutured was under tension. On August 11 the wound was slightly inflamed, and two days later the temperature began to rise, reaching 103° F. on the 15th and 105° F. on the 20th. On August 23 the temperature returned to normal and after that fluctuated. Lumbar puncture on August 30 produced blood and pus from which a pure culture of a coliform bacillus was grown. One month after the operation there was definite expansion of the skull and the infant was weaker. Head retraction was present and varied from day to day. Further lumbar punctures on September 8 and 26 produced "pure pus" and "turbid fluid" respectively. The infant died on October 25, 1934, aged 15 weeks.

Summary of Necropsy (*P.M.* 423. 1934). *Bronchopneumonia. Pyocephalus. Ascending purulent* (Bacillus coli) *cerebrospinal meningitis. Operation: Plastic repair of lumbo-sacral meningocele. Spina bifida.*—Slight œdema of myocardium. Œdema and congestion of liver, spleen and kidneys. Very little glandular tissue in thymus. Moderate amount of lipoid in suprarenal bodies. Severe mucous catarrh of stomach. Greyish green pus in both middle ears. An extremely wasted female infant.

Examination of brain.—The skull was slightly expanded, measuring 38 cm. in circumference, 22 cm. from nasion to inion and 28 cm. coronally between the external meati. The bones of the vault were widely separated. On opening the skull the convolutions were flattened and dry. During manipulation of the brain a considerable quantity (over 250 c.c.) of thin green pus escaped from the lateral ventricles. There were light adhesions between the arachnoid and dura at the base of the brain. Golden streaks of inspissated pus were present in the leptomeninges in the proximal parts of the Sylvian fissures and the adjacent surfaces of both temporal poles. Similar deposits were present over the dorsal and posterior aspects of the cerebellum and to a less extent on the ventral surface of the pons. The lateral ventricles were greatly dilated and the ependymal surfaces were coated with a thick layer of green pus. The cavity of the third ventricle and the Sylvian aqueduct were filled with inspissated golden pus. (The subtentorial part of the brain and the spinal cord were removed together with the dural theca and were fixed in formalin before further examination).

Apart from a diffuse chronic purulent spinal meningitis the principal features are illustrated in fig. 5. The cerebellum is well formed and appears to be of full size. The medulla oblongata occupies the uppermost part of the vertebral canal and is seen from the dorsal aspect as a smooth area (1 cm. long by 1·35 cm. from side to side) which is embraced on either side by the upwardly directed roots of the upper two cervical segments. This appearance of the medulla recalls the Arnold-Chiari malformation seen in the series of cases of meningo-myelocele, but on dissection there is no overlapping of the spinal cord by a tongue of folded medulla oblongata such as is seen in the fully developed malformation. Further dissection shows, however, a dislocation of the choroid plexuses of the fourth ventricle: a large tuft (0·6 cm. by 0·4 cm.) occupies the middle line between the tonsils in the position of the foramen of Majendie. From this the right choroid plexus loops downwards and forwards in the leptomeninges following the lower border of the tonsil and appears to terminate in the right foramen of Luschka. The left plexus is not visible from the exterior but lies within the ventricle, uniting the central intertonsillar mass with the left lateral recess. The cavity of the fourth

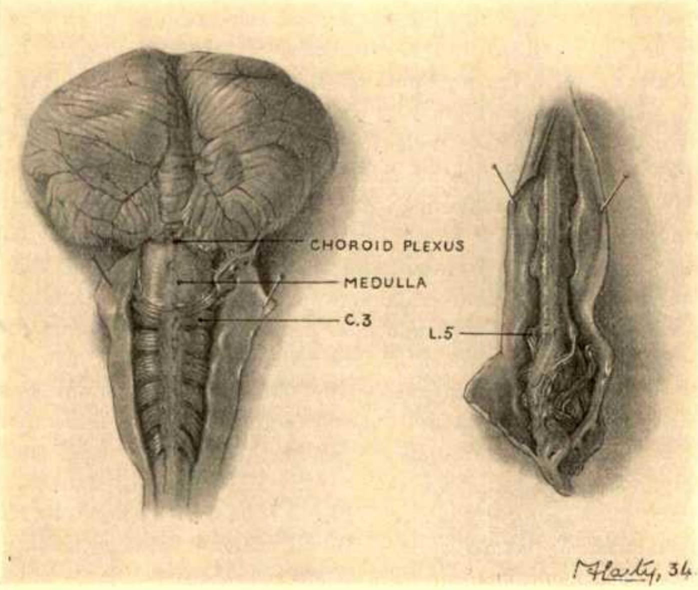

FIG. 5.—Dorsal views of hind-brain and lumbo-sacral cord in case of meningocele (P.M. 423, 1934).

ventricle is collapsed and is filled with inspissated pus. It is continued downwards just beneath the mid-dorsal line throughout the elongated portion of the medulla oblongata and passes thence to the central canal of the spinal cord, becoming more ventrally placed in the transition. The pons is well formed and is clearly demarcated from the medulla. The sulcus separating them is unusually low in relation to the cerebellum, being only 0·6 cm. above the tips of the tonsils. On transverse section the medulla appears well formed, the olives are present at the same level as the inter-tonsillar mass of choroid plexus and are traceable downwards to a point 0·2 cm. above the junction of medulla and spinal cord.

Spine and spinal cord.—A completely healed cruciate operation scar (7 cm. from above down by 5·5 cm. from side to side) extends from the second lumbar vertebra to within 1·7 cm. of the tip of the coccyx and laterally over the iliac crests. Beneath this is an oval deficiency (3·7 cm. long by 1·5 cm. at widest) due to the non-union of the laminæ of the lowest three lumbar and all the sacral vertebræ. This gap is filled in with scar tissue uniting the skin with the subjacent meninges. The appearances on dissecting the lowest part of the spinal cord are represented in fig. 5. The cord, which extended into the lowest part of the sacrum, ends in a bulbous expansion measuring 1·7 cm. from above down by 1·1 cm. from side to side by 0·6 cm. thick. There is no lumbar enlargement and no cauda equina. The lumbar cord is 4·5 cm. long and is similar in calibre to the thoracic cord. Its roots are given off almost horizontally and the lower filaments of the fifth segment are even cephalic in direction. The anatomy of the sacral roots was not satisfactorily elucidated, partly because the bulbous expansion was enveloped in scar tissue and partly, as transverse sections revealed, because an upward folding of the most caudal part of the cord led to an appearance of duplication just above the middle of the expansion and to a complete distortion of the pattern below this level. As shown in the figure, however, three roots pass in segmental fashion through the dura on the left side while two other roots cross the posterior surface of the expansion upwards and to the right to pass through the dura with the fifth right lumbar root and opposite the first left sacral root respectively. Throughout the thoracic and lumbar regions the centre of the cord is occupied by a lenticular or polygonal area (up to 0·3 by 0·1 cm. in the 4th lumbar segment) of yellowish appearance with, in places, a rusty-brown border.

Microscopic examination.—The leptomeninges throughout the spinal cord and the brain-stem show considerable fibrous thickening and are infiltrated with many plasma cells, small lymphocytes and a few neutrophil leucocytes. The central canal of the spinal cord and the cavity of the fourth ventricle are filled with similarly infiltrated, sclerotic tissue corresponding with the yellowish areas observed in the spinal cord with the naked eye. The yellowness is due to the presence of considerable collections of foam cells. These changes in the meninges, fourth ventricle and central canal are doubtless a result of the infection. The anatomical appearances described in the hind-brain and spinal cord are confirmed. The medulla is well-formed. Sections taken through the bulbous enlargement of the sacral cord at the levels of the left, second and third roots show, on either side, a deep lateral cleft. The outline of the cord thus resembles a flattened cottage loaf. In the more caudal of the two sections the spinal cord is almost completely divided into dorsal and ventral parts. The pia occupying the left lateral cleft in the higher of the two sections contains three epidermoid cysts, the largest of which (2 by 0·9 mm.) lies at the ventral lip of the cleft and the other two at the dorsal lip and the depth of the cleft respectively. The cysts are lined with squamous and prickle-celled epithelium and are filled with thin concentric laminæ of exfoliated material. They are evidently a developmental abnormality.

DISCUSSION.

We have described ten consecutive examples of the Arnold-Chiari malformation in cases of meningo-myelocele, and have shown how the deformity may be the cause of the hydrocephalus. In the literature upon the Arnold-Chiari malformation the exact nature of the spinal defect is not always stated. Thus in Arnold's one case the defect was described as a "Myelocyste," while in six of Chiari's seven cases it was simply labelled as spina bifida. Where, however, the nature of the defect is clearly stated it has been a meningo-myelocele.

Hydrocephalus is, however, also sometimes associated with meningocele, as is shown by clinical records. Such anatomical studies of this condition as we have discovered in the literature, and they have been very few, have not thrown any light upon the possible occurrence of malformations of the hind brain in this class of case. Nor have they given an explanation of the hydrocephalus which is sometimes found. Detailed descriptions of the central nervous system in spina bifida occulta have been published more frequently and there is no doubt that in this condition the hind-brain is usually normal. We have dissected the brain and cord in two examples of spina bifida occulta and in neither have we found any abnormality in the brain-stem. Hydrocephalus was absent.

Our single case of meningocele shows, however, that the incidence of malformations of the medulla oblongata and fourth ventricle of the Arnold-Chiari type is not limited to examples of meningo-myelocele. In the present instance it is clear that the deformities were of a far less severe order than those described as characteristic of the Arnold-Chiari malformation, although they appear to be of a similar kind. There was no hydrocephalus. The demonstration, however, of a minor degree of the malformation in a case of meningocele without hydrocephalus suggests the possibility that greater degrees of the malformation may be the cause of the hydrocephalus that complicates some examples of meningocele.

Our theory awaits confirmation. If hydrocephalus, either congenital or post-operative, were due to such a malformation, then air injected by the lumbar route would collect in the ventricles and not in the sulci upon the cerebral convexities. Such a result would be not only of academic interest but of clinical importance. It would point to the desirability of decompressing the spinal cord at the foramen magnum to facilitate the circulation of fluid in the leptomeningeal spaces. Such an operation has not yet been carried out.[1]

SUMMARY.

Attention is drawn to the Arnold-Chiari malformation as a possible cause of internal hydrocephalus in spina bifida.

The malformation was found in ten consecutive examples of lumbo-sacral or dorsi-lumbo-sacral meningo-myelocele.

A comparable but far less pronounced malformation of the medulla oblongata is described in a case of lumbo-sacral meningocele without hydrocephalus. It is suggested that a more typical Arnold-Chiari malformation may be the cause of the hydrocephalus that complicates some examples of meningocele.

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[1] Our attention has been drawn, while this paper was in the press, to a monograph entitled "Over Hydrocephalus," presented as a thesis for the doctorate in medicine in the University of Leiden by C. J. van Houweninge Graftdijk in 1932. The author discusses in this the probability that the Arnold-Chiari malformation acts as a valve, but he believes that it acts in a manner contrary to that suggested in our paper. He brings forward evidence that the cerebrospinal fluid can escape readily in an upward direction from the vertebral canal into the ventricles or cerebral meningeal spaces but has difficulty in passing from the ventricles down into the vertebral canal. He has endeavoured to relieve this obstruction either by resecting the tongue of redundant tissue or by resection of the bone over the posterior surface of the malformation and incision of the underlying dura. His cases, however, have died either from the effects of the operation or from post-operative complications.

PAIN: THE PERIPHERAL PATHWAY.

BY G. K. STÜRUP (COPENHAGEN)[1] AND E. ARNOLD CARMICHAEL.

IN order to explain the appreciation of pain in a limb apparently rendered analgesic by a lesion of the plexus or by section of the spinothalamic tracts, it has been suggested that pain impulses may utilize the periarterial plexus or sympathetic chain to gain entrance to the spinal cord.

In this paper are described experiments which were carried out to test these postulates.

EXPERIMENTS.

Two healthy young male adults were submitted to the following procedure:—

Subject A.—The left ulnar nerve was blocked by a perineural injection of a solution of 4 per cent. novocain, containing 1:100,000 adrenalin, where the nerve lies in the groove of the medial epicondyle of the humerus. When complete sensory loss in the distribution of the ulnar nerve was obtained, as judged by a failure to appreciate superficial and pressure pain as well as passive movement of the interphalangeal joints of the fifth digit, the digital artery and nerve at the ulnar side of the base of the fifth digit were exposed by open dissection. The artery with its adventitia was then laid, in a dry field, across two platinum electrodes connected to a secondary coil of a faradic battery. Stimulation was then applied to the artery with the secondary coil in various positions. During repeated stimulation of various durations and strengths no sensation of any character was perceived by the subject. The strength of the current used was more than sufficiently strong to give rise to pain when the electrodes were applied to the tip of the tongue and to contract the underlying muscle when applied to the skin. Stimulation of the exposed nerve in a like manner resulted in no pain or other sensation. The artery was then pulled, stretched and clamped with forceps again without resultant sensation. During the procedure pain and other sensations were appreciated from the radial border of the hand on appropriate stimulation.

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[1] This work was carried out on behalf of the Medical Research Council at the Research Unit, National Hospital, Queen Square, London, while Dr. Sturup held a Rockefeller Foundation Fellowship. One of the observations was reported in the Oliver-Sharpey Lectures, 1938, at the Royal College of Physicians by one of us (E.A.C.).

Doctors Robertson and Nevin kindly carried out the surgical procedure and to them we are grateful for their help.

Subject B.—A similar procedure was carried out with the following differences. The novocain solution was a 2 per cent. solution: after exposure of the artery and nerve, the artery alone was stimulated with a current from a secondary coil of a faradic battery. No conscious sensation was apparent during the stimulation, though at one time the electrical stimulus was much greater than necessary to produce contraction of muscle through intact skin.

Mr. Julian Taylor kindly carried out the surgical procedure and to him we are grateful.

CONCLUSION FROM EXPERIMENTS.

The perineural anæsthetization of the ulnar nerve as it lay in the groove of the medial epicondyle of the humerus produced a complete anæsthesia of the tissues supplied by the ulnar nerve distal to the site of the injection. It may be confidently asserted that the local injection of novocain did in no way reach the periarterial plexus surrounding the brachial artery as the latter lay anterior to the elbow-joint. The digital artery exposed at the dissection is a branch of the ulnar artery, itself a branch of the brachial artery.

Accordingly were there pain conducting fibres or fibres competent to carry impulses appreciated as pain travelling centripetally along the digital artery and its arteries of derivation, the novocain injection could not have reached them. As no pain or sensation resulted from stimulation of the openly dissected artery, it is only possible to assume that no centripetal sensory pathway from the digital artery was available along the digital, ulnar and brachial arteries, when the ulnar nerve was blocked at the elbow.

It is not to be assumed from these experiments that sensory fibres and endings are not to be found on arteries, for the evidence in favour of this is overwhelming. Pain resulting from experimental puncture of an artery is a well-established fact, also pain from the placing of hæmostatic forceps on an artery. The experiments described only afford proof that such sensory fibres travel but a short distance along the artery before they leave it to join a peripheral nerve.

DISCUSSION.

The literature dealing with the relief of pain by sympathectomy or by stripping an artery of its adventitia is of large proportions. The observations made by many have led to a controversy as to the presence or not of a possible pathway for sensory impulses from the periphery of the limbs by way of the periarterial network and sympathetic chain. It is not our purpose to review the literature in detail but to quote papers germane to the subject and in which excellent reviews of the literature may be found.

Were the hypothesis true that pain may be carried centripetally by such paths, anatomically it should be possible to establish the presence of fibres passing the whole length of an artery to the periphery of a limb. Busch (1927) in experimental histological investigations has demonstrated that in animals no nerves, either medullated or non-medullated, travel along the entire course of an artery from the main trunk to its peripheral branches. He asserts that both types of nerve reach their area of distribution at the periphery via the peripheral nerve trunks, Coates (1932) in dissections of the human produced evidence that the limb arteries as they proceed distally receive frequent branches from the peripheral nerve trunks. The anatomical evidence thus favours the view that pain is unlikely to be transmitted along the periarterial network from the periphery.

These anatomical studies have received confirmation in the work of Woollard and Phillips (1932) as regards the efferent vaso-constrictor fibres. By anæsthetizing the various peripheral nerve trunks of the leg and arm these two investigators were able to establish that vaso-dilatation occurred in the distribution of the nerve. These observations suggest that the efferent nerves to blood-vessels utilize the peripheral nerve trunks to reach their area of distribution. Further, Davis and Pollock (1930), in an experimental study with decerebrate cats, were unable to provoke any reflex activity by the electrical stimulation of arteries of a limb which had its nerve supply sectioned immediately distal to the rami-communicantes. They believe that any afferent stimulus in such a sensitive reflex preparation as the decerebrate cat would have elicited a reflex response : and they conclude that their experiments substantiate the view that there is no long afferent pathway from the limbs which utilizes the periarterial plexus and sympathetic chain.

Foerster (1927), Foerster, Altenburger and Kroll (1929) have made many observations upon patients who had pathological lesions involving various parts of the nervous system or who had had various surgical procedures carried out for the relief of pain. As the result of their intensive study, they deduced that the periarterial plexus may carry sensory stimuli from the periphery of a limb, and that the sympathetic chain may carry sensory impulses from the legs to enter the cord above the level of a spinal or root lesion. That their material was also pathological material renders the interpretation of the results obtained a task fraught with difficulty and some uncertainty.

The experiments recorded in this paper were carried out under physiological conditions, namely, no disease process was present, the subjects being healthy and the procedure was limited and exactly definable. It is our opinion that the described experiments are in accord with the anatomical evidence and favour the view that in man the periarterial plexus does not serve as an afferent pathway for pain from the periphery. It has thus been possible to establish that no pain impulses from the digits of the upper limb reach the central nervous system by passing along the periarterial nerves to the sympathetic ganglia, thence by the rami-communicantes to the posterior roots and so to the spinal cord.

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SHIVERING: A CLINICAL STUDY WITH ESPECIAL REFERENCES TO THE AFFERENT AND EFFERENT PATHWAYS.

BY V. UPRUS (TARTU), G. B. GAYLOR (GLASGOW),[1] AND
E. ARNOLD CARMICHAEL.

SHIVERING may be caused by a variety of circumstances, different in kind and degree but productive of the same type of muscular activity. The various causes of these movements, generally regarded as shivering, are toxic as in the course of fevers, visceral as in relaxation of the sphincters, emotional as in fright and thermal as in disturbances of environmental temperature. This study concerns itself with shivering produced by alterations in temperature and was undertaken to investigate the pathways subserving the afferent and efferent sides of the shivering mechanism.

In a series of investigations on dogs, Sherrington (1924) found that, on transferring an animal from a hot to a cold atmosphere, shivering occurred. If the animal had a spinal transection, shivering occurred sooner than in the normal animal and was more profound. There was, however, no shivering below the level of the lesion. When the paraplegic part of the animal was immersed in cold water, there occurred shivering independent of sensory stimuli from the part immersed. The conclusions from Sherrington's work were that shivering produced by cooling an animal was the result of changes in blood temperature acting on a "centre" higher than the spinal level, or the result of such blood temperature changes acting upon sensory endings in the intact region of the body and the consequent stimulation of a "centre" higher than the spinal level.

Dworkin (1930) found that shivering may occur in acute preparations after transections of the brain stem had been made as low down as 2 mm. cephalic to the calamus scriptorius of rabbits.

Keller (1933) found that shivering occurred in cats even when

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[1] This work was undertaken on behalf of the Medical Research Council at the Research Unit, National Hospital, Queen Square, London, while Dr. Uprus held a Rockefeller Foundation Fellowship and Dr. Gaylor a Halley-Stewart Research Fellowship.

transections of the medulla oblongata had been made. In the work of Penfield and Bazett (1924), shivering was not produced in chronic preparations of cats decerebrated at the level of the superior colliculi. It is difficult to make definite conclusions about work in acute and subacute preparations, but the general trend of this evidence points to existence of some cephalic "centre" necessary for the production of shivering.

METHOD.

Two series of studies were undertaken. A number of healthy men, chosen from a group of young post-graduates, were submitted to the following experimental procedure. The method employed was then adapted to the investigation of patients suffering from the effects of focal lesions of the central nervous system.

The subject was seated or lay in a semi-recumbent position with the whole body exposed to the surrounding air in a draught-free cubicle. Following a control period of twenty to thirty minutes, the legs were immersed up to the level of the tibial tuberosities in a tank of water kept at a temperature of 44° to 45° C. When adequate warming had taken place, as evidenced by general vaso-dilatation, increase of pulse-rate and frequently sweating, the legs were transferred as rapidly as possible to a tank of water kept at a constant temperature between 10° C. and 15° C. During the immersion in cold water, shivering manifested itself. The shivering, ushered in by a feeling of coldness and stiffness of the limbs, was permitted to continue until it was impossible to inhibit the clonic-like tremor by voluntarily relaxing or bracing the muscles. When the shivering had become uncontrollable, the legs were transferred to the tank of warm water until shivering ceased and peripheral vaso-dilatation had been initiated for a second time. At all times the water in the tanks was kept constantly circulating. During the course of the experiment the temperature of the skin at various sites on the body was frequently determined by means of thermocouples. A record of the rectal temperature was obtained by means of a special thermocouple inserted 5 to 6 cm. within the external sphincter.

The rectal thermocouple was of a particular type, designed to give rapid registration of temperature change. A hollow finger-like copper structure of low thermal capacity fixed to a vulcanite end grooved to permit the sphincter ani to close upon it, constituted the heat receptor from the rectal mucosa. Into the thin piece of copper were soldered two wires, one constantan and the other copper. In the rectal thermocouple a difference of potential proportional to the temperature of the copper was measured against a constant difference of potential in a second thermocouple kept at constant temperature of 37° C. The difference between the currents in the two thermocouples was registered on a high sensitivity mirror galvanometer. By means of a factor determined by physical experiment and found to be constant over temperature variations such as were recorded, the amount of deflection above or below a zero mark was translated into terms of temperature in degrees centigrade and subtracted or added to 37° C. Thus the rectal temperature was obtained at any point of time. The limitations of this method are a necessary lag on the part of the rectal thermocouple in virtue of thermal capacity, and a small lag, of maximum twenty-two seconds, in the galvanometer itself. Although no claim is made that the rectal temperatures recorded here are absolute, it is certain that changes of temperature are registered with reasonable rapidity, as can be seen by many of the findings. The principle of skin temperature recording was the same, but the applicability of a thermocouple directly to the skin surface obviated the necessity of a large surface couple and in registration a needle galvanometer was found sufficient. Readings of rectal temperature were made every fifteen seconds and skin temperature readings at about the same intervals of time. Direct observation was made of the time of onset and cessation, the distribution, the intensity and the character of shivering. Notes were also made of sweating and "goose-skin" when they occurred. The subject at the commencement of the experiment was invited to co-operate by informing the observer of any subjective sensation of warmth or cold which might be experienced.

OBSERVATIONS.

A. Normal Individuals.

Experiments were carried out on healthy individuals. During the period of control the skin temperature fell, except in the experiments when the air of the cubicle was kept at 37° C. or over; the rectal temperature remained practically level, in some falling over a period of twenty minutes, not more than 0·02° C., or rising even a smaller amount. After immersion of the legs in warm water for a period of five to fifteen minutes the skin temperature rose. The rectal temperature also invariably rose and before the rapid rise in skin temperature. The amount of rise in rectal temperature varied considerably, the smallest being 0·25° C., and the greatest 0·80° C. Following the immersion of the legs in cold water, skin temperature rapidly fell to as low a level as or lower than at the commencement of the experiment, except when the temperature of the air of the cubicle was kept high. When this was done little or no fall occurred in skin temperature, except when sweating had been present. The rectal temperature within one to three minutes following the transference of the legs to cold water commenced to fall rapidly. In two experiments a fall of 2·5° C. in rectal temperature occurred in twelve minutes: however, in the majority of individuals the registered fall averaged between 1° and 1·50° C. in ten to twenty minutes. After immersing the legs in cold water and at the time when the rectal temperature was falling, shivering commenced. The subject first complained of a cold feeling or "as if inclined to shiver"; this was succeeded by obvious shivering, at first in irregular outbursts in varying muscle groups, which rapidly became more intense and widespread. In the early stages the shivering could be caused to disappear either by

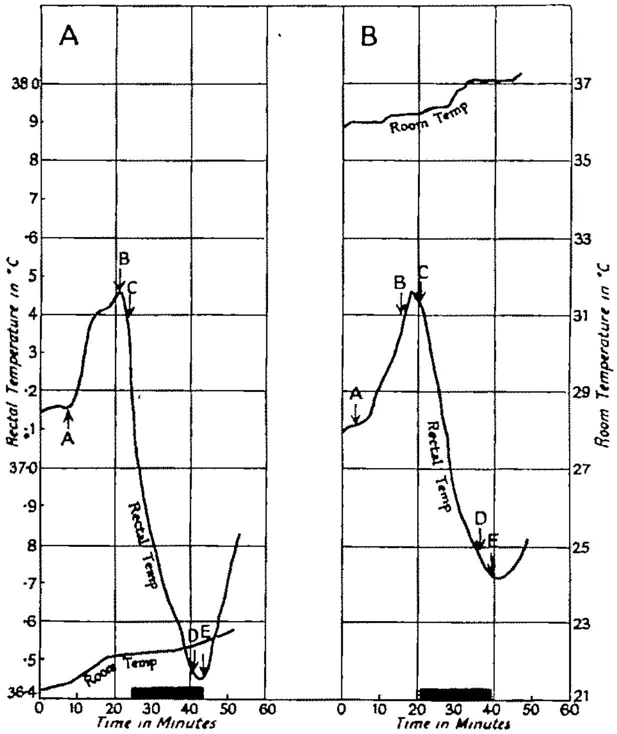

FIG. 1.—Normal. Chart A with low room temperature. A, legs into water at 45° C. B, legs into water at 9·1° C. C, commenced shivering. D, legs into water at 45·4° C. E, stopped shivering.

Chart B with high room temperature. A, legs into water at 45° C. B, legs into water at 12·1° C. C, commenced shivering. D, legs into water at 43·4° C. E, stopped shivering.

voluntary bracing or relaxing the muscles. Eventually the shivering became so intense that no effort on the part of the subject could control it. When the shivering had become uncontrollable, the subject was still able to perform voluntary movements, though these were frequently interrupted by the involuntary shivering; thus acts of precision were performed with the greatest difficulty.

On the legs being removed from the cold bath and placed in warm water, the rectal temperature gradually altered its gradient of fall and then commenced to rise. Nearly co-incident with the cessation of the fall and the commencement of the rise of rectal temperature, shivering ceased. The end of shivering was seldom abrupt—generally it became less severe, less widespread, then in irregular bursts, finally to cease altogether. It was striking to observe during this period an apparent relaxation suddenly come over the subject, which in time was coincident with the commencement of the rise of rectal temperature. It thus appeared that shivering was closely connected with the fall in rectal temperature and was independent of alteration in skin temperature resulting from the vaso-constriction produced by immersion in cold water. To elucidate this aspect two subjects were submitted to the same procedure, only differing in that the air of the cubicle was kept at 37° C. (fig. 1). In this way an attempt was made to avoid cooling of the skin, but owing to eruption of sweat it was not possible to prevent a slight fall in skin temperature. In spite, however, of the almost negligible fall in skin temperature shivering occurred under these conditions in the two subjects, and in every way was similar to that produced when the air of the cubicle was at a lower temperature.

B. *Subjects with Lesions of the Nervous System.*

(i) *Complete transverse lesion of the cord.*—In two cases observations were made, but in only one was the rectal temperature of sufficient accuracy to be of value for full analysis. In the first case, in which rectal temperature readings were inadequate, it was noticed that no shivering occurred below the segmental level of the lesion though reflex activity was present. Shivering of the type seen in normal subjects only occurred in muscles innervated from above the segmental level of the lesion. In the second subject who had a fractured spine with loss of reflex activity below the level of the ninth dorsal segment on the left side and tenth dorsal segment on the right side, shivering occurred when the legs, after previous immersion in warm water, were immersed in cold water. Only those muscles having a nerve supply from the segments above the level of the lesion showed the irregular movements of shivering. The onset of the shivering occurred during the fall of the rectal temperature at the tenth minute after immersion of the legs in cold water. Following the transference of the legs to warm water shivering ceased three minutes after the rectal temperature began to rise, though the actual rectal temperature was 0·99° C. below that registered during the control period when no shivering was manifest (fig. 2). It is of interest that before shivering was observed the subject complained of a cold subjective sensation in the upper part of the trunk.

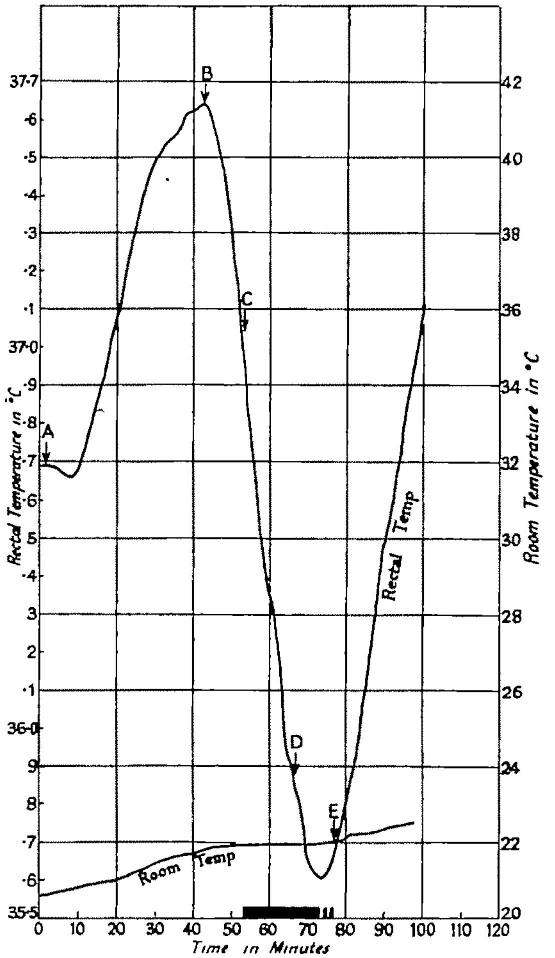

Fig. 2.—Complete transverse lesion of the cord. A, legs into water at 44·5° C. B, legs into water at 9·8° C. C, commenced shivering. D, legs into water at 44·4° C. E, stopped shivering.

From these two observations it is apparent that not only must the muscles in which shivering occurs have their motor innervation intact, but also that shivering as produced in these experiments is dependent upon a central mechanism at a higher level than the spinal segment. Further, these two experiments demonstrate that the shivering so produced is initiated not by sensory impulses passing centrally from the immersed limbs, but by cooled blood traversing the tissues above the level of the segmental lesion. In the discussion this will be more fully dealt with.

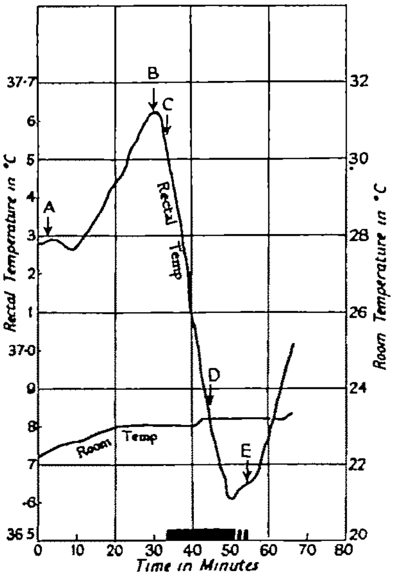

FIG. 3.—Hemiplegia. A, legs into water at 45·2° C. B, legs into water at 9·8° C. C, commenced shivering. D, legs into water at 44·2° C. E, stopped shivering.

(ii) *Lesions involving the pyramidal tract in the cerebral hemisphere.*—Five subjects were studied. The degree of motor involvement varied from a slight paresis to a marked weakness with great spasticity. In all, some voluntary movement remained. It was possible to produce shivering in the muscles of both the healthy and paretic side of the body in all subjects. The shivering had the same relationship to the fall of rectal temperature, and ceased in the same manner when the rectal temperature commenced to rise, as in normal subjects (fig. 3). In two subjects the shivering manifested itself first on the hemiplegic side, but in the remainder it commenced either on the sound side or on both sides at the same time. Coincident with, but sometimes preceding the shivering, the hemiplegic limbs became more rigid, the upper limb contracting so as to become flexed and adducted.

The study of these cases demonstrated conclusively that damage to the pyramidal tract in no significant way influenced the character, time of onset, or cessation of shivering. These experiments did not offer conclusive proof that the mechanism of shivering was independent of the pyramidal tract as in all subjects there remained some degree of voluntary movement. It appeared unlikely, however, that the pyramidal pathway was necessary as the degree of hemiplegia did not influence in any way the character of the shivering or its temporal relationship to the rectal temperature.

(iii) *Lesions involving the thalamus.*—In subjects suffering from symptoms and signs referable to a lesion in the region of the thalamus, no demonstrable difference occurred in the time of onset and cessation, the distribution or intensity of shivering on the two sides of the body.

It becomes evident that loss of conscious sensation from one half of the body does not influence the mechanism associated with shivering.

(iv) *Lesion of the cerebellum and cerebellar pathways.*—The lesion in one case investigated was, so far as could be determined clinically, as purely cerebellar as possible. A long history of years of incoordination was present and the case presented the features of a primary atrophic lesion of the cerebellum and its connections. By the method described, shivering was produced which in time of onset and cessation, severity and distribution, was the same as in normal individuals. The relationship between these events and the rectal temperature was in essence similar to that found in the normal condition. A remarkable phenomenon was observed in this case, in that although shivering occurred the movements were modified from the clonic-like type to choreiform movements. In another case with a unilateral lesion of the cerebellum the temporal relationship of the shivering and rectal temperature were identical, and on the side of the lesion the shivering was of a choreiform type.

An intact cerebellum appears a necessary requirement for the production of the clonic-like movements of shivering.

(v) *Bilateral cordotomy.*—A subject who had been operated on two years previously was investigated. The spino-thalamic tract on the left side was cut at the third dorsal segment and on the right side at the fifth dorsal segment. The subject had a complete sensory loss to pin-prick, heat and cold up to the segmental levels incised. The deep reflexes in the legs were brisk and the plantar responses were extensor.

The subject, however, had excellent control of his legs and was able to walk several miles a day without the aid of support. In this particular subject, shivering was induced with ease, the period of latency between cold immersion and the onset of shivering being very short (fig. 4). Shivering was limited to the muscles innervated from segments above the level of the incisions in the cord. Even with profound lowering of rectal temperature it was not possible to induce shivering in the muscles innervated from segments below the incisions in the cord.

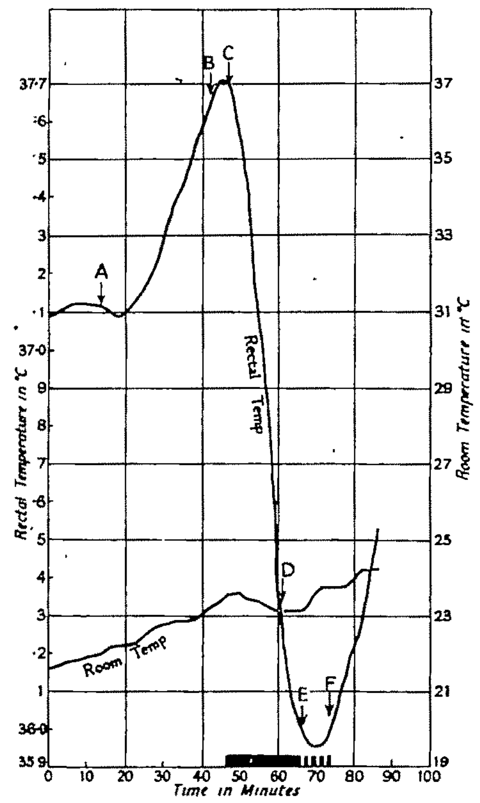

FIG. 4.—Cordotomy. A, legs into water at 45° C. B, legs into water at 10·6° C. C, commenced shivering. D, legs into water at 45° C. E, relaxation observed. F, stopped shivering.

This case demonstrates that in the presence of slight dysfunction of the pyramidal tract shivering does not occur. By deduction it would appear relevant to suggest that the efferent mechanism of shivering is dependent upon the integrity of tracts lying in close approximation to the spino-thalamic such as the tecto-spinal and rubro-spinal.

DISCUSSION.

In these experiments rectal temperatures were recorded at a distance of 5 cm. from the sphincter. While it is impossible to state categorically that the temperature at such a level is that of the circulating arterial blood, it is unlikely that it can be otherwise. Consequently for the purpose of the discussion the rectal temperature recorded has been accepted as indicating the arterial blood temperature and will in the discussion be referred to as the blood temperature.

From the investigation of normal subjects, the constancy of production of shivering during a phase of rapid fall in blood temperature suggested that in normal shivering changes in blood temperature might be of significance. Two positive findings were of constant occurrence: first, the period of latency between the application of the sensory stimulus of cold to the immersed limbs and the onset of shivering; second, the cessation of shivering near the lowest point on the blood temperature curve which occurred sometime after the legs had been immersed in warm water. Only in one instance did shivering cease at the point of transference of the lower limbs from cold to hot water. The period of latency between cold immersion and commencement of shivering is against the view that the mechanism of shivering is entirely reflex unless summation of stimuli is invoked to explain the occurrence.

The type of shivering produced in these investigations of normal people ceased after the limbs had been heated for some time but not before there was some definite alteration in the rate of fall of blood temperature or a definite rise. This fact was again suggestive of the possibility that blood temperature played an important part in the causation of shivering. It must be made quite clear that the mechanism producing shivering as described above is the only mechanism under present consideration. It is known that the shivering of febrile conditions occurs with a rising internal temperature—an observation which was confirmed in the present series of studies by making a continuous record of rectal temperature during a malarial rigor. This mechanism is probably of a different character although objectively there appears to be no difference in type of movement. Again the sensory function as productive of shivering is admitted; an immediate and transient response to an extreme but indifferent thermal stimulus is characteristic of well-established reflex activity operated without change in blood temperature. It is unlikely that such immediate but transitory shivering as occurs on immersion in a hot or cold bath can be brought about by a change in blood temperature.

The proof that change of blood temperature may cause shivering lies in the investigation of paraplegic patients. In these cases no possible sensation travelled up from the legs. Further the sympathetic chain may be excluded as being a possible afferent pathway. The only mechanism whereby shivering was produced depended therefore on some alteration in the state of circulating blood. There is no evidence to suggest that this alteration was of a chemical nature and the fall in internal temperature was so striking and so constantly associated with shivering that it was believed to be the causative factor.

If a fall in blood temperature is the effective stimulus to such shivering as was produced here, a consideration of the possible sites of action has to be undertaken. These possible sites are: (1) Directly on muscle; (2) directly on spinal segments; (3) on temperature endings originating impulses to be conveyed to a "centre"; or (4) a "centre" itself without an afferent nervous pathway.

The first and second possibilities are excluded by the fact that paraplegics do not shiver below the level of the lesion. The impulse to shiver must be dependent upon a mechanism higher than the spinal level, and shivering is not an intrinsic response of muscle to cooling blood.

There remain two ways in which such a falling blood temperature may act through the medium of the nervous system: (*a*) On a centre in the brain sensitive to temperature change; (*b*) on thermal endings remaining in communication with the entire nervous system.

The proof of either hypothesis was beyond the limitations of the material at our disposal. The following fact, however, may be of importance. It was easy to make the case of cordotomy shiver above the sensory levels. If the skin endings were in reality the afferent end of a reflex pathway, the motor expression of which was shivering, it is natural to assume that the greater the area of intact skin the easier it is to make the individual shiver. In the case of the patient with cordotomy, the intact skin area was confined to the head, neck, arms and shoulder girdle regions, but he shivered as readily and as intensely as did the normal individual. This piece of evidence is against the second hypothesis. The same argument holds as evidence against endings in situations other than in the skin being the effective afferent end of the shivering arc. If the direct stimulation of a "centre" cannot be admitted, then a separate thermal receptor in the brain or in a situation unaffected by any of the lesions in the present series, has to be postulated. In spite of the doubt about the exact nature and site of operation of the effective affector stimulus, the existence of a "centre" higher than the spinal level must be inferred. No attempt is made to localize that "centre" directly because we have no evidence pointing to its primary involvement. Certain deductions may be made by argument from the results obtained.

Shivering occurs on both sides when the pyramidal tract has suffered insult. The amount of shivering in respect of excursion of the tremor is, if anything, a little greater on the hemiplegic side. Shivering occurs apart from pyramidal tract integrity. Shivering in a patient with cerebellar disease is strikingly modified to a choreiform tremor. It is natural to conclude that such a modification indicates some dependence of normal shivering upon intact cerebellar pathways.

In one case there was a lesion of the thalamus; the localisation of the lesion was confirmed by X-rays which showed a calcified mass in the right thalamus. When this patient was made to shiver there was no deviation from normal appearances and there was no difference between the tremor on either side. The further observations on hemiplegic patients with definite thalamic signs showed normal shivering to the usual stimuli. These findings point to the shivering mechanism being independent of the thalamus.

Most instructive is the case of cordotomy in which there was no shivering below the level of the lesion. In this case the absence of shivering must be due to interruption of spinal pathways. Physical examination revealed that there was interruption of the spinothalamic pathways and some interference with extrapyramidal tract conduction.

Absence of shivering cannot be accounted for by the interruption of spinothalamic pathways since there is no deviation from normality so far as shivering is concerned when there is thalamic disease. The slight interference with pyramidal path conduction is not adequate as an explanation because it has been shown that shivering occurs when the pyramidal pathways have been interrupted.

Interference with cerebellar pathways cannot be held responsible because there was no shivering, whereas it has been seen that shivering of an abnormal type occurred when the cerebellum itself was diseased. The only pathways left to consider are the extrapyramidal such as the tectospinal and rubrospinal. These tracts descend in the spinal cord in areas which would be sectioned by cordotomy. We may, therefore, conclude that they constitute the pathway by which the impulses of shivering (originated in the brain-stem either directly or indirectly by the falling blood temperature) reach the muscles.

SUMMARY.

A method is described of inducing shivering constantly in normal subjects.

The relationship between the onset and cessation of shivering to rectal temperature change is discussed.

Cases with manifest disease of the central nervous system were made to shiver and the responses observed.

From the investigations it has been shown that shivering, as produced by the constant method described, is independent of pyramidal thalamic and cerebellar integrity, although the type of tremor produced is modified by cerebellar dysfunction.

The conclusion is reached that the effective stimulus is a falling blood temperature acting directly on a "centre" or on a thermosensory mechanism capable of stimulating the shivering "centre." The downward pathway from the "centre" is by exclusion shown to be an extrapyramidal pathway, either the tectospinal or rubrospinal.

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NOTE ON THE NATURE OF THE MOTOR DISCHARGE IN SHIVERING.

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THE rapid fluctuations in the muscular contractions of shivering appear to the eye to vary in speed from relatively slow contractions to rapidly repeated shaking closely resembling the clonus of spastic muscles. The character of the movement changes from time to time and from place to place in the limbs. To seek more closely for any relationship between the character, location and intensity of the movements in different regions we have recorded them from jaw, thorax, biceps brachii, and quadriceps femoris, concurrently. For this purpose a small light balloon was attached between the teeth, others over the belly of biceps brachii and quadriceps, where they were held by a piece of adhesive strapping to the skin over the remaining belly of the muscle, and a band around the thorax at the level of the nipples compressed also a further balloon. The pressure within each balloon was registered optically by manometer and mirror and recorded on a moving strip of bromide paper. In three experiments the action currents of biceps brachii or quadriceps were also registered on the same strip of paper. Shivering was induced by rapidly cooling the right upper and lower limbs by ice water after the subject had been warmed until sweating had occurred. The left limbs, from which the records were made, were rested in a natural posture of semi-flexion.

As the body temperature falls the first indication of onset of shivering was usually an isolated twitch of the masseter, on one occasion of the whole thorax. This preliminary twitch is followed by others at very variable intervals of 0·2 seconds to 1·6 seconds. The first onset may be a small series of three or four twitches rapidly repeated. If the shivering be gradual in onset, presumably from slower fall of temperature, these single twitches occur in one muscle or another for many seconds before the next change occurs. In one or other muscle, usually first in the masseter, series of such twitches are repeated rapidly at rates from 4 to 6 a second for a period and such bouts of clonic twitching then gradually increase in length (figs. 1 and 2). At this time the twitching in the upper and lower limb continues to be single or in sparse groups (fig. 1). The shivering at this and later stages can be caused to cease immediately in any particular muscular group by voluntary contraction of that group (figs. 1, 2 and 3). It can also be ceased by voluntary restraint, not necessarily but usually with some slight bracing of some part of the body and cessation of respiration (fig. 3). Passive movement of a limb lessens the movements of that limb, but complete voluntary relaxation is difficult if not impossible to maintain during this procedure.

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[1] Halley-Stewart Research Fellow, Halley-Stewart Research Fellow, and Rockefeller Foundation Fellow respectively.

As the twitching becomes fused into clonic outbursts in each muscular group the respiration becomes irregular, with periods of apnœa. At this time one or other muscle may still continue twitching.

The intensity of shivering in any particular muscle group, together with the time of onset of shivering, appear to be related mainly to the amount of other contraction present. A muscle completely at rest shows early twitching and early fusion of twitches. A maintained posture, however slight, delays the onset of shivering.

A voluntary movement in the more intense stages of shivering is followed by greater outburst of shivering in the muscles concerned (figs. 2 and 3). Similarly a deep breath is accompanied by partial or complete subsidence, and followed by increased shivering for an interval (fig. 4). As the intensity increases the respiration deepens and the periods of apnœa lessen so that regular breathing is reasserted. The periods of clonic twitching increase in length, and the intervals shorten, until one or other muscle commences continual repetitive clonic movements at the rate of 4 to 6 a second (fig. 3).

The twitching, and the periods of rapidly repeated clonic contraction are not coincident in time in any two of the sites examined. The rate of rapid beating varies from time to time in any one muscle group, and when two are beating concurrently there is no correspondence in their rates (figs. 5, 6, 7 and 9). The smaller muscles usually contract more rapidly, and movements at the hip and shoulder are slightly slower than in the jaw or distal joints of the limbs. When recovery occurs after the voluntary suppression of severe shivering the commencement of the clonic movement is also independent in each muscle, both in time and in frequency (fig. 9). When all the musculature is affected, however, there occur intervals when the clonus of many muscular groups becomes synchronous for periods of at first one or two seconds and later for longer. This appears to be the maximum development of shivering, a "shuddering" movement of the trunk and limbs. It will be observed, however, that even here some groups, for example, the closing muscles of the jaw in fig. 6, remain independent in rhythm. At this stage the subject has the greatest difficulty in abolishing the movement by effort of will. Richet [2], in discussing the maximal rate of repetition contraction in muscle, stated that the rate of tremor in shivering was about 10 to 11 beats a second, and did not exceed 13 a second. We have not encountered rates as high as this, slightly over 6 beats a second being the highest observed frequency.

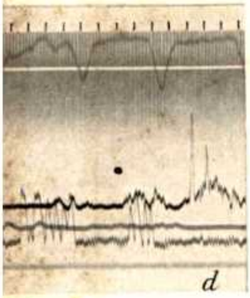
The action currents of shivering movement, as recorded by a Matthews oscillograph, reveal single diphasic waves for many of the first twitches, with the early appearance of small groups, in some of which identical wave forms are repeated at intervals of one-twenty-fifth second, suggesting that the slightly longer twitches are small tetanic contractions. These become brief tetani of three-fifths second to one second duration. For long intervals the discharge may now become sparse but regular, as in slight postural tone. Gaps in this discharge corresponding to the beats of concurrent clonic contraction in other muscles occur only when the generalized shudder occurs (fig. 7). Sooner or later the action currents become grouped into dense volleys separated by quiet intervals, corresponding to the regular alternation of the clonic beats (fig. 6). In each such beat complete fusion of the action currents into one large electrical variation was not at any time seen, a feature which is in sharp contrast to the electromyogram of the reflex clonus of spastic muscles. The general appearance of each outburst in any one muscle in shivering suggests strongly that there is rapidly repetitive discharge in each motor unit for each beat, rather than that single impulses in each fibre group were out of phase in each volley as in reflex clonus.

We have recorded reflex clonus in the lower limb of two patients suffering from a spastic paraplegia, concurrently with the outbursts of shivering in the upper limb and mandible. We were unable to demonstrate any interruption or change in type of the clonus in the lower limb. Voluntary contraction converts the clonic discharge of shivering into a continuous one, without any stage in which the voluntary contraction itself becomes clonic, as occurs in the presence of reflex clonus. The clonus of shivering and that resulting from damage to the pyramidal tract differ, therefore, not only in the nature of discharge, but in relationship to cold and to voluntary movement.

The suppression of shivering by voluntary effort is not always accompanied by contraction in the shivering muscle, and the action currents may cease completely as in fig. 8. The subject feels that he achieves the cessation by a general relaxation, and the effect may be purely inhibitory. Nevertheless, cessation of respiration occurs, and this probably indicates some contraction of the musculature of the trunk.

The myographic characteristics of the type of shivering brought about by rapid cooling of the skin surface, therefore indicate a movement which has independant development in each muscular group concerned. This independance affects both the manner and the time of development, and would suggest a local segmental mechanism for its production. The experimental investigations of Sherrington [3] have demonstrated the limitation of shivering to the headward segments of the dog with spinal transection, both in response to lowered blood temperature and to direct cooling of the skin of the segments concerned. Our experience with patients suffering from transverse lesions of the spinal cord has also convinced us that the central control of shivering is cephalic. The movements of the panniculus resembling shivering which were reported by Goltz [1] to occur in the isolated segments of the spinal animal in response to direct stimulation of the skin by cold, have not been obtained by others [2, 3] despite careful research. There therefore appears to be no basis for the assumption that shivering can occur as a segmental spinal reflex. At a stage of high intensity the rhythm of shivering becomes identical in almost the whole musculature, and this "shuddering" necessitates the presence of a co-ordinating mechanism to secure the identity of the rhythm in widely-spaced parts. The independent manner in which the movement develops in each muscular group therefore has more probable explanation in the varying states of the spinal motoneurones brought about by voluntary and postural factors, and affecting at each the manner in which discharge occurs in response to one cephalic nervous mechanism. Just as a strained posture of a limb results in delay in the appearance of the movement in that limb, so slight differences in posture combine with the discharge of shivering so as to alter its rhythm. This change of rhythm does not occur to any obvious degree with reflex clonus in spastic muscles, but we maintain that shivering is a separate and distinct repetitive movement. The manner in which shivering gives way to

PLATE X.



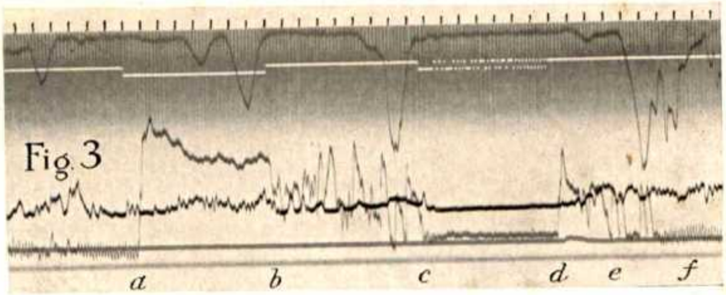
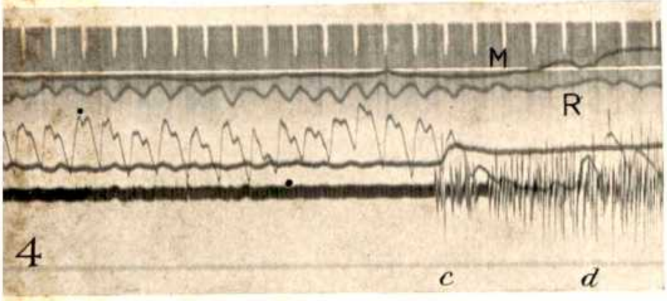


Fig. 3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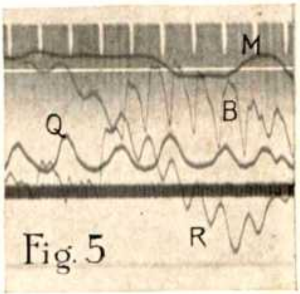
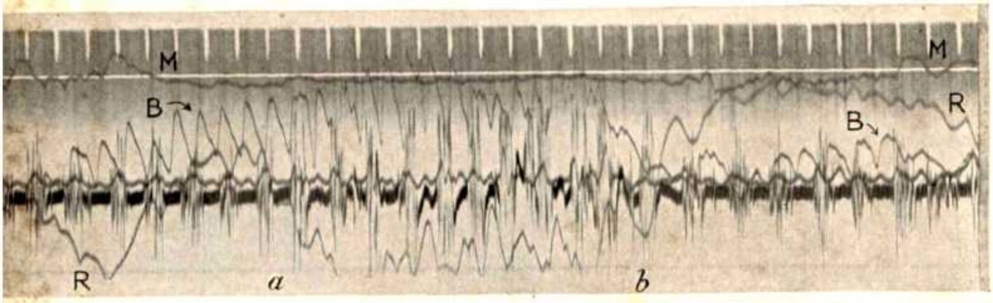


Fig. 5



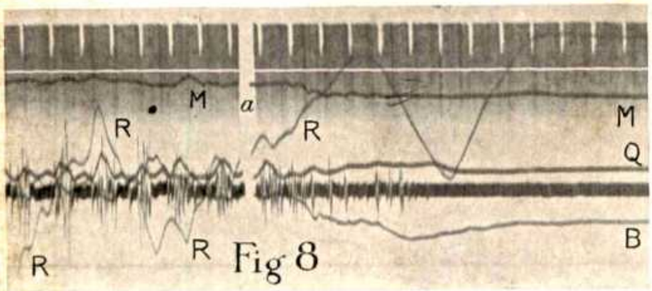


Fig 8

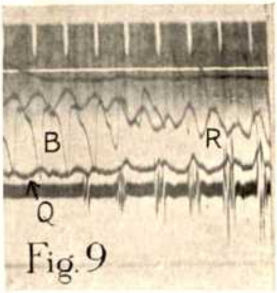


Fig. 9

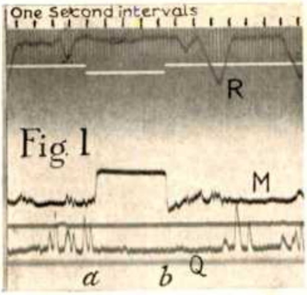


Fig. 1

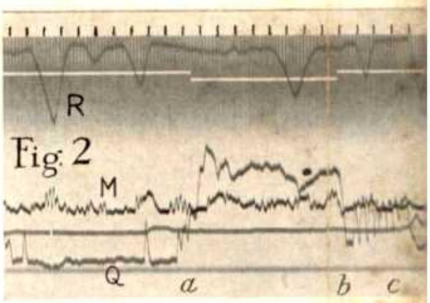
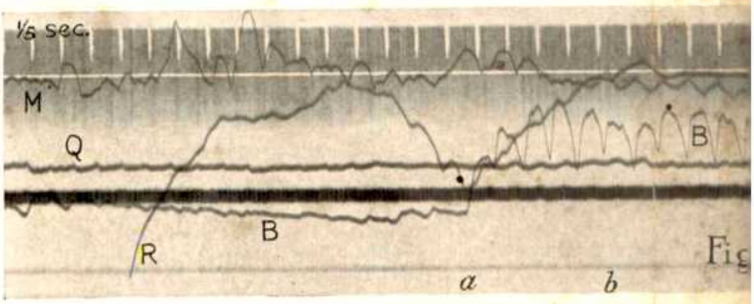


Fig. 2



Fig

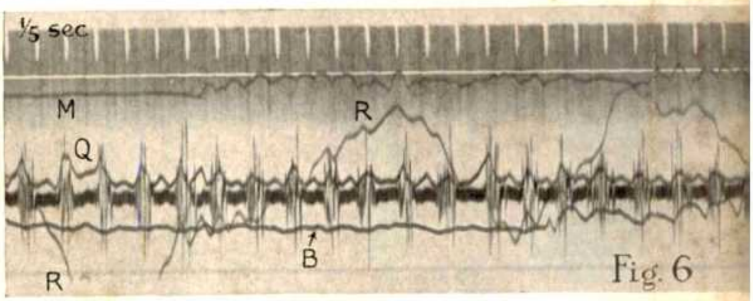


Fig. 6

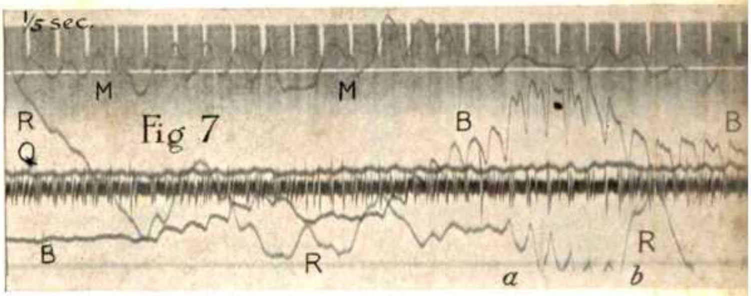


Fig 7

To illustrate paper by D. Denny-Brown, J. B. Gaylor, and V. Uprus.

voluntary movement allows it to fulfil the requirements of promotion of metabolism without the necessity for particular posture or interference with willed effort.

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DESCRIPTION OF PLATE.

MYOGRAPHIC RECORDS OF SHIVERING FROM THE NORMAL SUBJECT.

All figures read from left to right.

FIG. 1.—Shortly after the commencement of shivering, showing movements of the thorax (R), of closure of mandible (M), and of contraction of quadriceps extensor (Q). The twitching has already fused into small series in the mandible, while more isolated twitching is still occurring in quadriceps. Between *a* and *b* the subject clenches the jaw voluntarily. The time marking for such record has been stressed by a small black vertical line above the record at one second intervals.

FIG. 2.—As fig. 1, thirty seconds later, showing periodic apnœa and more continuous series of clonic twitching in the jaw. From *a* to *b* the knee was extended voluntarily to order.

FIG. 3.—As figs. 1 and 2, thirty seconds later. Quadriceps now shows continuous fine clonus. From *a* to *b* the knee was extended voluntarily, and from *c* to *d* the subject suppressed shivering by voluntary effort.

FIG. 4.—More rapid speed of recording. A vertical white line marks each one-fifth second. The broad dark horizontal line is the record of a Matthews oscillograph, recording action currents from quadriceps. At the commencement of the record the subject has just made an involuntary deep inspiration and as the respiratory recorder (R) returns to the record, the movements in the mandible (M) increase in amplitude, and a prolonged outburst commences at *a* two seconds later in biceps (B), with some clonic movement at the same rate in the pectoral muscles, seen as an alteration in the record from the thorax (R). The movement in the mandible ceases at *b*. At *c* a series of action currents in quadriceps extensor results from voluntary contraction. Their continuity is not affected by the rhythm of contraction in biceps at *d*.

FIG. 5.—As fig. 4. An outburst of shivering in biceps (B) and pectorals (R) occurs during a slower rhythm of flexion at the hip (Q) which was recorded indirectly by the balloon over quadriceps. There is no contraction at this time in quadriceps.

FIG. 6.—Record as fig. 4. Showing the electromyogram of clonic discharge in quadriceps with independent outbursts in the mandible (M) and biceps (B), with coincidence of the rhythm in biceps, pectorals and quadriceps from *a* to *b* with general "shuddering."

FIG. 7.—Records as fig. 4. Showing a more tonic type of contraction in quadriceps (Q), with some grouping corresponding to an outburst in biceps brachii between *a* and *b*.

FIG. 8.—Records as fig. 4. Voluntary suppression of discharge commencing at *a*.

FIG. 9.—During the recommencement of discharge ten seconds after fig. 8.

THE DISSOCIATION OF CORTICAL EXCITATION FROM CORTICAL INHIBITION BY PYRAMID SECTION, AND THE SYNDROME OF THAT LESION IN THE CAT.

BY SARAH S. TOWER.

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EXPERIMENTS on the motor cortex, such as stimulation or ablation, have commonly been interpreted in terms only of excitation or destruction of the cortico-spinal neuron. This practice Dusser de Barenne's (1934) recent work on laminar thermo-coagulation of the cortex seems to justify. Yet clinical neurology has persistently emphasized differences between the effects of cortical lesion and lesion of the cortical projection paths. True, these are more clear-cut on the sensory side than on the motor in the discrepancy between the thalamic syndrome and that of the somæsthetic cortex. Yet even on the motor side cortical and subcortical lesions, both involving the pyramidal tract, are certainly not equivalent. Nor is this to be expected. Obviously the cortical lesion entails destruction of a multitude of longer and shorter association neurons, together with the projection neurons. Moreover, the projection neurons are by no means a single tract, as Poliak's (1932) recent studies again show, but have supra-segmental as well as segmental destinations. Furthermore, the Betz cell neuron is not itself a simple cortico-spinal neuron, but a complex structure sending off collaterals at the level of the pons and perhaps into the corpus striatum. According as a lesion of the pyramidal system destroyed such pre-spinal projection neurons and collaterals or left them intact, its effects might well differ. With these considerations in mind the present research was designed, first, to evaluate the consequences of lesions of the pyramidal tract below its last large supra-segmental connection to the pons, and then to determine the activity of still surviving supra-segmental projection neurons and cortico-spinal collaterals by comparison of the effects thus produced with the familiar results of a cortical lesion, and by electrical stimulation of the motor cortex after degeneration of its segmental projection tract.

MATERIAL—PROCEDURES.

Ten adult cats in which the right pyramid had been cut at the level of the trapezoid body provided the material for study. Under ether anæsthesia a ventral approach along the lateral wall of the pharynx exposed the occipital bone between the bullæ tympani and the edge of the foramen magnum. Through a hole in this bone, 8 or 10 mm. long and half as wide, the dura and pia were slit, the basilar artery retracted to the left, and a fine knife inserted exactly in the mid-line, at the mid-level of the trapezoid body and to the estimated depth of the pyramids. The cutting edge was then rotated to face the right pyramid, and the lesion made by drawing the knife upward in an arc to its lateral edge, visible as a deeply marked groove containing a small vein. To ensure the completeness of the lesion, the knife was then inserted at this lateral border and swept over to the mid-line. The operation was virtually bloodless at all stages. The animals made a remarkable recovery, showing neither shock nor excessive excitement. In an hour or less they could run and jump and behaved, except for the specific effects of the lesion, as any cat subjected to anæsthesia for forty minutes. The only post-operative complication was a transitory difficulty in swallowing.

Of the series of 10 cats 5 were killed at three weeks, 3 in the sixth month and 2 at the end of a year. Four of these last 5 were subjected to secondary ablations of the motor cortex of one side some time before death. In all the animals but one the motor cortex of each side was thoroughly explored electrically either just prior to ablation or to death, or at both times. After death by ether the vascular system was flushed with salt solution and the material fixed by the intra-aortic injection of Müller's fluid. The brain and cord were removed to Müller's fluid and later examined by the Marchi or Pal-Weigert method as required.

Examination of the brains before removing the specimens showed that all the lesions had been correctly placed over the trapezoid body and had completely severed the right pyramid without injuring the left. In one animal the brain had herniated into the bone defect. With lesions of months' standing the right pyramid was reduced to a flat strand below, while the left remained of normal size unless the left motor cortex had also been removed. The shrinkage following cortical ablation did not, however, in any case equal that resulting from the lower lesion.

OBSERVATIONS ON THE LIVING ANIMALS.

The functional deficit of pyramid section.—One description will suffice for the series of cats, for with one exception all elements of the syndrome were demonstrable in every animal at all times, from two hours after the operation throughout the survival period, even to a year. The effects of the lesion were appreciable only in the contralateral limbs, the axial musculature escaping except for a transitory deviation of the tail to the normal side. Homolateral symptoms were totally wanting. The lesion disturbed the normal balance of flexion and extension in progression, the fore and hind extremities being used stiffly with little or none of the characteristic triple flexion. Consequently the animals limped, for a time the toes on the side of lesion dragged, and either as an integral result or in compensation a circumduction of the hind developed, resembling that of a hemiplegic man. In running and jumping the stiffness was frequently so great as to throw the animal towards the normal side. Accompanying this stiffness was weakness, unmistakable during the first few days as a tendency for the affected limbs to give way as the body's weight came to rest on them; and later, apparent only as the animals stood at rest, in a "knuckling under," as it were, of the foreleg at the wrist, suggesting imperfect fixation at this joint.

Corresponding defects appeared in posture. A normal cat held in the air by head and tail extends all four extremities, or when suspended by the hind or fore legs it extends those left free. The cats with unilateral pyramid lesions likewise extended the free legs equally on the two sides. But given support for the back, or when held in the air somewhat longer, flexion supervened in normal limbs, while those affected by the lesion remained extended. This occurred too when the animals were slung in a hammock in the upright position, the legs being thrust through holes. Extensions was often retained even when the animal had begun to climb out, a procedure invariably initiated by the limbs of the normal side.

With the cat lying quietly supine on lap or table this sequence was again repeated; an extension, initially symmetrical, became asymmetrical through flexion of the normal legs. From a few seconds to as long as ten minutes were required for the difference to mature, and the quieter the animal the slower its development. In this posture in which the animals were comfortable, a feature of the maintained extension was its passive quality, which was obscured by the tenseness of animals held in the air. The flexion of the normal legs was active immediately prefacing an attempt at righting or in general preparedness. These extremities opposed a correspondingly great resistance to passive extension while co-operating in flexion. In contrast, the behaviour of the affected legs was almost neutral, neither flexion nor extension being much resisted, and flexion, once passively imposed, was commonly retained. The apparent hyper-extension of the crossed limbs thus appears as a normal extension abnormally prolonged because of a deficiency in flexor activity.

In postural reactions in the more precise sense, as studied by Magnus, Rademaker and others, the selectivity of the defect for certain flexor activities was again exhibited. For example, in the "Sprungbereitshaft" of Magnus the downward thrust of the legs of an animal dropped suddenly through space was executed equally on the two sides in the presence of unilateral pyramid section, but the flexion which terminates this extension if the descent be halted in mid-air was lacking in the crossed limbs. Again, as an animal was slowly lifted from a surface, a leg lacking cortico-spinal innervation lost contact first, not from any deficiency of extension, which was symmetrical, but because certain small movements which operate continually to keep the normal foot in the best position for contact were wanting. The larger flexion which follows in a normal leg when contact is finally broken, and which is sometimes clearly aimed at placing the foot on the nearest object, was also wanting.

Analysis of the defect in these two instances brings clearly into view what was suspected in the initial study of posture and gait. The basic postural mechanism of extension is intact, symmetrical and not overactive, but a large group of preparatory and terminal movements, movements of adjustment and correction, largely flexion, are diminished or wanting. The absence of these produces the abnormalities of posture. These movements all partake of the nature of placing reactions. Further study was pursued along the lines laid down by Bard (1933), and his analysis of the cortical control of the placing and hopping reactions was used as a standard against which to assess the effects of subcortical lesions on the same mechanism.

Of the five placing reactions described by Bard, only four were examined in the presence of pyramidal lesions. These were: (1) Placing of the feet in response to contact of the dorsum of each with a table edge; (2) replacing the fore or hind feet after they have been thrust over a table edge; (3) replacement of a leg passively abducted; and (4) placing of the fore-feet on the edge of a table when the chin of the animal is brought to rest upon it. The fifth reaction, placing in response to stimulation of vibrissæ, which necessitates the enucleation of the eyes, was omitted in favour of the visual placing reaction described by Bard and Orias (1933). The hopping reactions were also studied; these were elicited by horizontal displacements of the animal's body through space, either backward or forward or from side to side, as corrective movements to keep the extremities which must be in contact with the table directly under the body.

Before proceeding to describe the deficiency in these reactions following pyramid lesions, it may be pointed out that the first three placing reactions and the hopping reaction are elicited by stimuli from below the level of the lesion, and largely from the leg concerned. The chin-on-table reaction and visual placing, on the other hand, originate above the level of the lesion. Hence, inadvertent sensory destruction, in particular of the medial lemniscus, may interfere with the former reactions, but not with the latter.

In this study, as in Bard's, defect in the placing reactions appeared first as clumsiness of gait and oddities of posture. In running the paws turned under, or the legs slipped to the side, front or back. In standing or sitting the legs likewise slid out of position, the fore and hind limbs often scissoring. Such abnormalities were uncorrected. Examination of the special placing reactions showed that the entire group was gravely impaired. The first reaction, that to contact of the dorsum of the paw with table edge or finger, suffered most, being virtually extinguished. If, however, a proprioceptive stimulus were added to the tactile, by moving the animal horizontally to the table until the extended limb was passively displaced, a reluctant placing could generally be obtained, at least after the first days. The amount of passive displacement required (measured with a protractor) decreased progressively during the first month or two, and in one animal up to the fourth month after operation. But finally a threshold was established, between 20° and 60°, which remained fairly constant for each animal under standard conditions of examinations (animal quiet, unfatigued, in good health, and weather not too hot). This represents the only quantitative data on recovery obtainable in these experiments. The remaining three cutaneous-proprioceptive placing reactions had to be recorded only as present or absent. Under the so-called standard conditions of examination they were almost invariably absent, the chin-on-table reaction equally with those originating in the limbs. After the first week or so, by making the animal angry or excited, all three reactions could be brought out, though always sluggishly and clumsily compared with the normal. Fear, on the contrary, suppressed these reactions, even in normal animals.

The hopping reactions followed the course just described in that after a brief period of complete depression they made a variable, and indeed, somewhat better recovery. After a time, usually a month or two, their condition became stationary with a result which differed from animal to animal, chiefly owing to differences in temperament. At best the recovery was imperfect, wide and uneven spacing of the steps remaining as permanent evidence of the lesion. Moreover, this recovery was not stable, for hot weather, illness or subsequent operation immediately brought about a return to the previous state.

The condition of visual placing presents an interesting problem, for, as Bard and Orias (1933) have shown, this reaction survives ablation of the sensorimotor cortex and is abolished by removal of the area striata. Section of the pyramid greatly reduced it. Indeed, with both fore-legs free the normal only was placed. Only if the normal limb was restrained, or the animal excited and eager to escape to the table, was the leg affected by the lesion brought into play. This effect of the lesion on a reaction using corticifugal pathways other than those from the motor area does not, however, necessarily reopen the question of the origin of the pyramidal tract, which Holmes' and May's (1909) Nissl studies, on cats among other animals, showed to be co-extensive with Betz cell distribution in the cortex. The effect of the lesion on the excitability of spinal centres, which will be analysed later, offers a simpler explanation of this result.

Examination of placing and hopping does not, however, exhaust the functional defect from pyramid lesions in cats. There remains a general deficiency of usage of the limbs quite outside these reactions, the full extent of which has probably gone unappreciated, but which was unmistakable in the animals' two most characteristic activities, namely, pawing induced by curiosity and the clawing of anger. Both these activities were permanently diminished on the side opposite the lesion. Indeed, when both legs were free, the preferential use of the normal was so great that only excitement brought the other into play. Then, however, its execution was indistinguishable from the normal. In this general deficiency of usage the flexor and extensor elements in movement suffered together, though not equally.

Such further consideration of the effects of a pyramidal lesion in terms of defective or lost unit reactions still fails, however, to reveal one common aspect of the movements effected which the condition of the scratch reflex immediately after operation brought into sharp relief. One animal showed this especially well. She had an ulcer behind the left ear and prior to operation scratched it freely using the left hind-leg. When this was attempted after operation, the leg was brought up into the extended position well if somewhat stiffly, but the series of alternate flexions and extensions which would have effected the scratch presented difficulty. In several trials nothing but the most trifling flexion could be attained. Finally, after the right hind-leg had been requisitioned without relief, the first three or four movements were executed, and thereafter the series followed with increasing ease and range. Clearly, the postural element of the reflex was intact, and only its phasic element impaired. This is true of other movements, for, whether in gait or in placing or hopping reactions, or in the more complex activities of pawing and clawing, the movement lost is phasic in character. The tonic or postural activities survive, neither impaired nor exaggerated, but apparently quite normal.

That the results of pyramid lesion are not complete, but partial loss of function should now be clear. In the case of the scratch reflex, just cited, the phasic movements were finally executed when relief was not obtainable in any other way. Likewise, in placing and hopping, pawing and clawing, if the stimulus were of sufficient intensity or imposed upon a background of sufficient general excitation the reaction followed. Conversely, general depressing factors, such as illness or hot weather as well as the specific inhibition of fear, suppressed all the reactions under consideration, even on the normal side. Whether a given reaction was obtained or not became in final analysis a matter of summation of excitation and inhibition at the final neuron.

The attempt will now be made to analyse the effects of unilateral pyramid section at this level. One set of reactions was particularly useful in this analysis. This was the reflex flexion which a normal cat gives as threshold response to pricking a paw pad or pinching the tips of the toes, which is attended in the fore-legs by blinking of the eyes. Severing one pyramid permanently increased the strength of stimulus required for the flexor response on the opposite side. Indeed, this was the most stable sequel of the lesion. However, the operation spared the cortical facial innervation, and conserved the normal low threshold for blinking on stimulation of either fore-paw, although with this strength of stimulation only the normal leg flexed. Certainly no sensory defect is involved here. The only interpretation is that the flexion reflex, the archtype of spinal reflexes, is normally under reinforcement from the cortex. In the words of the Sherrington school the cortex, via the pyramidal system, contributes to the central excitatory state of the flexor motoneuron pool, probably continuously, but perhaps only at the moment of elicitation of the reflex. By this much the excitatory state which must be built up by incoming volleys of sensory impulses is diminished and threshold held low. Pyramidal lesions, by eliminating the first source of excitation on the opposite side necessarily increased the amount of afferent stimulation required for the reflex. Comparison of the myotatic reflexes of flexor muscles on the two sides showed a like inequality of threshold. The widespread flexor and abductor responses obtained bilaterally from a single stimulus, as percussion over the sacral spines, were commonly weaker on the side affected by the lesion. Clearly, then, the spinal flexor mechanism had suffered a general loss of excitation which impaired any action utilising it.

This effect of pyramidal lesion on the flexor centres of the cat's cord is obviously commensurate with the large flexor representation in the cat's cortex, as revealed by electrical stimulation. Similarly, then, the spinal extensor centres might be expected to suffer a small loss of excitation in proportion to the meagre cortical representation of extension. This was not demonstrable. To casual inspection indeed, the contrary condition of increased excitability seemed to result. But the hyperextension pervading movement and posture has already been resolved into an ordinary degree of extension, inordinately maintained. The lack of excessive rigidity in this extension, as gauged by the resistance opposed to passive flexion, has been pointed out.

No good superficial extensor reflex could be found for study, and even the myotatic reflexes, with the exception of the knee-jerk, proved difficult to standardize. With the knee-jerk, however, consistent results were obtained throughout the series of animals, and for the duration of the experiments. On the side affected by the lesion the reflex was larger and longer enduring than on the normal side, and occasionally this leg retained a residue of the extension. Yet if the animal relaxed during examination the difference between the sides diminished, until on the verge of sleep the jerks became symmetrical, and both of the loose type previously characteristic of the side opposite the lesion. Clearly, the original difference between the sides was due to the operation of active flexion in checking the normal jerk and the lack of such flexion on the incompletely innervated side. Certainly the contralateral spinal-extensor centres were not depressed. The occasional tendency to retain extension after the knee-jerk might again be taken as evidence of the opposite state. But the lack of clonus in the post-operative syndrome and of a clasp-knife phenomenon, indeed the conspicuous absence of all signs of spasticity, together with the very moderate resistance opposed to passive movement, sufficiently demonstrate that severing the pyramid had not increased the excitability of the spinal-extensor centres as does the hemiplegic lesion of man.

The failure of the extensor centres of the cord to be appreciably depressed by section of the pyramid is not surprising, for the methods of testing were crude. Indeed, the weakness and poor joint-fixation previously alluded to may be this depression in another aspect. On the other hand, the failure of the lesion to reproduce the hyper-excitability of the extensor mechanisms, which is the basis of spasticity in the hemiplegic condition of man, involves other considerations. These may more profitably be pursued after the evidence from cortical ablation and stimulation has been presented.

Having raised the question of a possible contribution of sensory disturbances to the total functional defect, the measures taken to evaluate this complication may be briefly discussed. The selection of the trapezoid body as the level of lesion was dictated by the desirability of interposing an indifferent structure between the lesion and the presumably deeper-lying ascending tracts.

To get a measure of the effect of proprioceptive lesions, the right posterior column was cut in the first cervical segment in two animals, and these were studied by the same methods as the animals with severed pyramids, one of them for a year. Pal-Weigert preparations confirmed the completeness of the latter lesion. The consequences of this operation for the placing and hopping reactions, and for posture in general, resembled in kind the effects of section of the pyramid, but were less in degree; the same general deficiency in the use of the legs appeared. With the passage of months, however, only a preferential use of the incompletely innervated extremities in placing, hopping, pawing and clawing remained to indicate the presence of a lesion. Certainly, therefore, the more lasting effects of the pyramid section may be ascribed to destruction of the descending pathway rather than to inadvertent injury to the ascending sensory systems, even one neuron higher up.

The manifold and enduring losses of function following upon section of the pyramid may then be accepted as those of a cortico-spinal lesion. Whether expressed in terms of unit reactions—placing, hopping, pawing or clawing—which were found to be deficient, or in the more general terms of loss of excitation at the final common neuron, the full extent of the defect has probably gone unappreciated. As it stands, however, certain features characterize it. First, the effect on flexor and on extensor mechanisms is unequal, in conformity with their unequal representation in the motor cortex. Secondly, phasic movements are impaired with the preservation of the tonic or postural. These results might both have been expected. On the other hand, the absence of spasticity, and indeed of evidence of release of any lower mechanism, is a notable feature in the syndrome, upon which the results of cortical ablation and stimulation throw some light.

Secondary ablation of motor cortex.—Six months after the original operation, when the resulting symptomatology seemed stationary, one motor cortex was exposed in four of the five still surviving animals, explored electrically and excised. In two animals the cortex removed was on the side of the original lesion, and after three weeks additional survival these were killed for Marchi preparations. In the other pair, the contralateral cortex was ablated. These animals were allowed to survive for six months, when they were then killed and examined by Weigert's method. The objects of these ablations were chiefly anatomical, e.g. Marchi preparations to check the completeness of the cortico-spinal lesion, and Weigert to reveal any admixture of fibres other than cortico-spinal in the pyramid.

Study of the living animals after these secondary ablations was most suggestive. When cortical removal was superimposed on section of a pyramid, there remained, after the post-operative exacerbation of the old symptoms had passed off, a slight but definite rigidity in the affected legs as a new contribution to the syndrome. When the new lesion was contralateral to the original one, the results were greater and more complex. At first, placing and hopping were improved on the side opposite the original lesion, and abolished contralateral to the cortical lesion. Later these reactions became equally deficient on the two sides. The gait, however, was not thus rendered symmetrical, for wider circumduction still distinguished the limbs affected by the pyramid lesion. The superficial reflexes and the flexor myotatic reflexes had high thresholds on both sides, whereas the knee-jerk and the positive supporting reaction were more easily elicited and extension was longer maintained in the limbs opposite the cortical lesion. Even six months later, a lesser mobility of the extremities opposite the cortical lesion and a slightly greater resistance to passive flexion remained to indicate that the abnormality produced by the cortical lesion was in some way graver than that established by the subcortical lesion. To be sure, these experiments are few in number and the quality they deal with, namely spasticity, is a subtle one. In time the series will be extended. Yet inadequate as they are, the results of stimulation of the cortex lend them support and invest them with a significance sufficient to warrant their being put on record.

Stimulation of the motor cortex.—The motor cortex of both sides in all the cats but one was explored electrically, either previous to ablation or before the animal was killed. The extent of any previous cortical ablation was also checked by re-stimulation. The stimulating was performed under light ether anæsthesia, with a unipolar electrode delivering a 60 cycle sine wave current. The apparatus (designed by Mr. Myers) permitted determination of threshold in terms either of voltage or of current. Posture played a decisive rôle in the results. The first five animals were studied in the usual manner—back up, legs dependent. Thereafter the position was reversed and the stimulating done in that stage of ether anæsthesia which produces an extension simulating decerebrate rigidity.

From the normal cortex the usual movements of the contralateral fore and hind legs were obtained, chiefly of flexion, but as progressively lighter anæsthesia was induced, there was increasing bilateral and extensor activity. The responses in the face, eyes, tongue and jaws were initially bilateral. When the cats were in the supine posture, however, the threshold effect of cortical stimulation was not contraction, but a relaxation of any tonic or clonic extensor state present in the limbs—gravity serving to demonstrate the relaxation. From 0·25 to 0·5 volts more was commonly required to produce active flexion from the same point. In these circumstances the cortical pattern in the cat is constituted of points which are inhibitory to extension and excitatory to flexion, with the former possessing the lower threshold of activity. Extensor points are so few and unstable in the cat's cortex and a flexor tonus such a rare state, that a corresponding investigation of extensor excitation and possible flexor inhibition could not be made.

When stimulating the cortex after division of its projection path at the level of the trapezoid body, the position of the animal and the depth of anæsthesia were all important. The first five routine stimulations demonstrated the preservation of the cortical facial and trigeminal innervations. And in one animal (No. 10) the lateral border of the anterior sigmoid gyrus gave a curious slow retraction and flexion of the opposite fore-limb, and that was all. On the other hand, the last four stimulations performed with the animal lying supine and with the legs tonically extended or in clonus, gave quite another result. For now from the presumably "silenced" sigmoid gyri, relaxation of the extensor tonus or clonus was obtained, and in a pattern corresponding to the fore and hind leg patterns of the normal cortex. But on increasing the strength of the stimulation this relaxation was not followed by flexion, as in the normal, but only by more rapid or more enduring relaxation. The relaxation or inhibition of extensor tone thus obtained was never instantaneous. The limb did not flop, but gradually over many seconds, the rate depending both on the amount of the extensor tone and on the strength of the stimulus, the extended limb relaxed, but only while the stimulation was acting. Indeed, by applying and removing the electrode, relaxation could be made to proceed in a cog-wheel fashion. Moreover, against a strong extensor tonus or clonus, inhibition might last only for the duration of the stimulation and not always even for that, the extensor centres frequently escaping. Relaxation was obtained with equal facility from the normal cortex, and at a slightly lower threshold. In cat 13, for example, relaxation of extensor tone in the hind legs on the normal side occurred at 1·75 volts, and on the side on which the pyramid was divided at 2·0 volts. But the flexion which supervened on the normal side with any increase of stimulus above threshold limited the study of inhibition there to the threshold response. Exploration of the cortex contiguous with the motor area, especially of the gyrus proreus and the entire convexity of parietal, occipital and temporal lobes, with voltage up to that producing generalized contractions, revealed no other region exercising this inhibition. The number of these successful stimulation experiments, like that of the ablation experiments, is few, but a second series of crucial experiments has already confirmed and amplified the original findings.

The evidence assembled now seems to offer an explanation of the absence of spasticity, or of "release" in any form, from the syndrome of a pyramidal lesion, and also of the differences between the effects of section of a pyramid and of cortical ablation. Apparently, excitatory and inhibitory effects of cortical activity are dissociated, in large part at least, at some prespinal level. The excitatory component is then transmitted directly to the spinal cord along the cortico-spinal tract, while the inhibitory component must be relayed through prespinal centres, finally to reach the cord along other descending pathways. The small difference in the inhibitory threshold between the normal cortex and that on the side of pyramidal section may indicate that the prespinal dissociation was less than complete. The pyramidal section, by destroying the first excitor component which is largely flexor, produced the manifold deficit described, one aspect of which was uninterrupted extension. Yet by preserving virtually intact the second inhibitory component, the syndrome was kept free of evidence of subcortical release, as rigidity and spasticity. These are the additional contribution to the syndrome of cortical lesion when both components of cortical function are destroyed.

Previous work, notably that of Graham Brown (1913), Weed (1914), and Cobb, Bailey and Holtz (1917) has dealt with pre-spinal inhibitory mechanisms of the cortico-ponto-cerebello-rubral variety and other work, Rademaker's (1926) for instance, has shown that in cats, at least, the rubro-spinal tract serves inhibition to the cord. The augmenting influence of hemi-decerebellation on the excitability of the opposite motor cortex, first reported by Risien Russell (1894), likewise fits into the concept of a cortical inhibition exercised through the cerebellum. And certain aspects of cerebellar disease in man are in conformity with this view. Although the cortico-pontine collaterals of the pyramidal system offer a possible anatomical pathway for such inhibition, the present study has, in fact, provided no evidence to indicate either what pre-spinal course inhibition pursues, or whether systems of collaterals, or of independent neurons, or both, deliver inhibition to the presumed pre-spinal centres. If multiple systems be used, as for instance a cortico-striatal system, a cortico-rubral and a cortico-ponto-cerebello-rubral, lesions at different levels in the brain-stem might well produce different syndromes. This would seem to be the case in man. If, on the other hand, only one system is involved, the results of brain-stem lesions should be simpler. Further analysis will be required to determine how the inhibition operates. Nor is it unlikely that the complexity of the mechanism may vary in different species. The present study provides a point of departure only in the study of cortical inhibition, in the demonstration that in part at least, and that a large part, this threshold activity of the motor cortex is still exercised after destruction of the cortico-spinal pathway below its last large supra-segmental connection.

ANATOMICAL STUDY.

The central nervous system alone came under anatomical scrutiny. No contracture or atrophy developed in the skeletal musculature, nor disturbance in any other organ to give indication for further exploration. Investigation of the central nervous system was organized to determine the site and extent of the descending degeneration which it was the specific aim of the original lesions to produce, and secondly, of the ascending degeneration which might be the concomitant of this. To determine the descending degeneration sections were taken at the medullary level just below the trapezoid body, and from the C_7 and L_4

spinal segments. Sections through the lesion and just above, or at the decussation of the pyramids, were sometimes examined too. In looking for ascending degeneration sections from the middle third of the pons and from other levels up to the thalamus were prepared in two animals. Standard Marchi or Pal-Weigert technique was used according to the post-operative survival time, and serial sections were cut at 15μ.

The descending degeneration (figs. 2 and 3) demonstrated the unilaterality of the lesions. With the exception of the animal in which the brain had herniated into the defect in the skull, and a tiny medial strand in one other brain, the degeneration was confined to the pyramid on the side of lesion. The lateral limit of the degeneration was also strikingly constant; only its depth varied. Just below the level of the lesion the disappearance of fibres from the pyramid was complete. More caudally, fibres and bundles of fibres appeared in the field of degeneration. These, seen best in Weigert preparations, swung in in arcs in the plane of section, obviously in the course of the strands sweeping down from the nuclei of the posterior column. In the lateral column of the spinal cord the now crossed degeneration reached the lumbar region in considerable density and throughout the cervical region scattered degenerated fibres were unmistakable in the right lateral column in the position of the pyramidal tract in cases in which the left pyramid was demonstrably intact. Descending systems other than the cortico-spinal were entirely free of degeneration.

The ascending degeneration, on the contrary, involved several systems (figs. 1 and 2). In the cortico-spinal system retrograde degeneration varied considerably from a mere scattering of blackened fibres in the pons to a fairly dense degeneration, with traces up the brachium pontis on both sides. The anticipated destruction in the lateral lemniscus was fairly equally distributed to the two sides. In the medial lemniscus the degeneration, although variable, generally exceeded expectation; it was bilateral, but much heavier on the side of lesion. And here it was traceable in diminishing density to the ventrolateral border of the thalamus (fig. 1). The small crossed degeneration in the medial lemniscus may be ascribed to the strands of internal arcuate fibres which were seen swinging through the pyramid on the side of their origin, but the massive homolateral degeneration requires a more substantial basis. After removal of the motor cortex, the corresponding pyramid was far from depleted of fibres, as may be seen by comparison of the two sides in fig. 5. Yet at the cervical level the degeneration on the two sides were approximately equal. If the surviving fibres in the one pyramid be those contributing the ascending degeneration to the lemniscus, as seems most likely, then the pyramid, like the cortex, is a mixture of the ascending and descending systems which are the afferent and efferent pathways for the same body of reactions. And the physiological controls in the sensory component assume increased importance. Yet the constancy of the descending degeneration stands in contrast with the variability of the ascending, to indicate again that the remarkably standardized syndrome of pyramid section must depend upon the correspondingly standardized motor destruction.

More important to the argument developed in the physiological section of this paper, and based on the retention by the motor cortex of inhibitory activity while its excitor function is lost following severance of a pyramid, is the question as to whether the pyramid contains all the fibres of motor-cortical origin reaching its level. On this point secondary ablation of this cortex, six months after a pyramidal lesion of the same side, affords information. Deep to the pyramid, and extending lateral to it, is a field of fibres, chiefly the lemniscus with an admixture of fibres of cortical origin sufficient to give a new Marchi reaction. Many of these fibres are cortico-cerebellar, swinging back, even far caudally in the medulla, as Swank has described (1934). Occasional fibres were traced to the inferior olives. Still others went into the reticular formation, perhaps to cranial nerve nuclei. But none appeared to penetrate to the cord, not even in the specific instance in which stimulation of the cortex had evoked a motor reaction in the fore-limb. In view of the fact that inhibition was equally effective on extensor states in the fore and hind limbs, and, after the conditions necessary for its demonstration were fully appreciated, quite constant from animal to animal, the occasional cortico-spinal fibre which may survive pyramid section, cannot be responsible for the inhibition so vigorously exercised by the cortex.

COMMENT.

Severing the pyramids is an experiment which has been tried repeatedly, from Starlinger's (1894-97) early attempts on dogs to Barron's (1934) recent work with rats, and Marshall's (1934), with cats. Marshall's most recent paper has reviewed this literature in detail. The more rigorous standards now adopted in assessing the degree of recovery and of residual motor defect have made necessary this repetition of a simple experiment. That the standards are still imperfect is illustrated by comparing Marshall's latest report with the present study. Further repetition of the experiment as knowledge of cortical activity enlarges and means of testing improve, will, it is certain, demonstrate that the present observations are still imperfect.

The main contribution of the present study to an understanding of the sequels of a lesion in the voluntary motor pathway is the discovery of the pre-spinal dissociation of the inhibition and excitation of cortical origin, with the destruction of the latter function, only, by section of the pyramid. A second contribution has also been made in the demonstration that the effects of this pre-spinal lesion are in their entirety not transitory, but are probably permanent. On this, which is a fundamental point involving the plasticity of the cortex, the present study departs most widely from the observations and conclusions of previous workers. Yet even so, Marshall's (1934) recent study of the effects of lesion of the pyramid on the placing reactions foreshadowed this in the incomplete recovery found months after operation in some of his animals in certain aspects of their deficiency. The source of this discrepancy probably lies in the lesions produced, for the ten prepared for this study seem to be unique in their unilaterality and completeness. Certainly time was allowed in these for recovery beyond that permitted generally by previous investigators of such lesions.

A year, or even six months, is a relatively long period in the life of a cat, yet for such a time each element of the original syndrome with one minor exception remained demonstrable. Recovery was quantitative and unstable. Certain original difficulties, such as dragging the toes, were overcome by circumduction of the limb. On the other hand, many specific reactions were depressed and the general usage of the limb diminished for the duration of the experiments. At the level of the final neuron the crude test of the response to pin prick showed, after the first few days, no further recovery in the raised threshold of the spinal flexor mechanism. Certainly the defect was easily compensated, either by increased strength of stimulation or by raising the animal's general level of excitation. Highly organized reactions exhibited a large degree of spontaneous improvement. Yet the more carefully the fundamental defect was disentangled from the complex pattern of even the simplest action, the more stable did the syndrome appear, until ultimately in such analysis the irreparability of the physical lesion was expressed in the permanent disability of the living animal.

SUMMARY.

The right pyramid was cut at the level of the trapezoid body in ten adult cats, and secondary ablation of motor cortex was performed in four cases. During survival periods of from three weeks to a year the animals were observed, and at some time the motor cortex of both sides was stimulated electrically. Subsequently, specimens of brain-stem and cord were prepared by Marchi or Pal-Weigert technique for studies of degeneration.

The loss of function may be described either in terms of specific reactions such as placing and hopping, pawing and clawing which were lost or diminished ; or it may be expressed as a loss of phasic activity, chiefly flexor; or again it appears as a raised threshold of the spinal flexor centres. In any form, it is permanent. The extensor mechanisms of the cord are not appreciably affected.

Secondary ablation of motor cortex adds to the syndrome of the pyramidal lesion a degree of rigidity, hitherto absent.

Stimulation of the motor cortex demonstrates the retention there of inhibitory activity, with the loss of excitation, indicating a pre-spinal dissociation, in large part at least, of these two elements of cortical function.

Anatomical studies showed descending degeneration confined to one pyramid, with a large crossed and a small uncrossed component in the lateral columns of the cord. Ascending degeneration involved the lateral lemnisci of both sides and the medial lemniscus chiefly of the side of lesion. This degeneration of the medial lemniscus is ascribed to the commingling of ascending with descending fibres in the pyramid, making this like the corresponding area in the cortex, a sensori-motor system.

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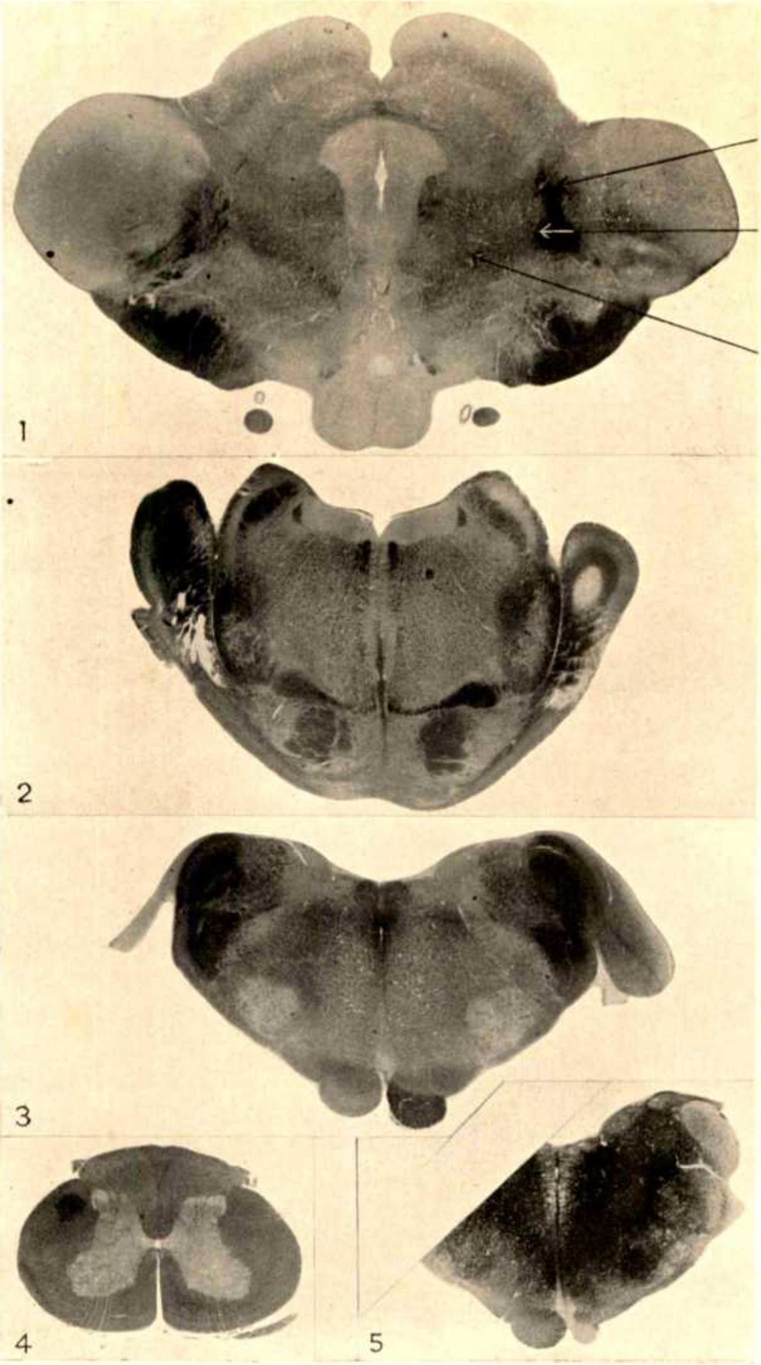
PLATE XI.



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DESCRIPTION OF PLATE.

Figs. 1-5.—Marchi preparations showing the ascending and descending degenerations produced by a lesion of the pyramid of three weeks' standing.

Fig. 1.—Transition from midbrain to thalamus; degenerated fibres scattered throughout the ventrolateral tegmental fields where indicated by the arrows.

Fig. 2.—Middle third of pons; scattered degeneration throughout the entire lemniscus system, densest in the right medial lemniscus.

Fig. 3.—Medulla; below the trapezoid body; degeneration of the entire right pyramid.

Fig. 4.—C7; degeneration in the left corticospinal tract.

Fig. 5.—Pal-Weigert preparation of the medulla below the trapezoid body, taken six months after ablation of the left motor cortex and one year after sectioning the right pyramid, and showing the unequal effect of these lesions on the pyramids.

AN INVESTIGATION OF THE NERVOUS CONTROL OF DEFÆCATION.

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I.—INTRODUCTION.

THE investigations of Hurst [19] have established that inefficiency in defæcation commonly results from nervous diseases and is accompanied by fæcal accumulation in the rectum (dyschezia). The delivery of fæcal material to the rectum in these cases is not functionally impaired. To the lack of sensation of desire for defæcation and consequent absence of voluntary effort, Hurst attributes the greater part of the disturbance. Appropriate voluntary effort does not suffice to correct the defect. The mechanism by which the sphincter ani is normally induced to relax is not clear, and is commonly attributed to spinal reflex activity of some kind, possibly stimulated by movement within the colon [11], assisted by willed straining. The diminished tone of the anal sphincter consequent to lesions of the sacral innervation gives reason for the prevalent view that a spinal "centre" for defæcation lies within the sacral segments, and that complete fæcal incontinence in this type of nervous lesion results from loss of the sphincteric mechanism. Even in complete transverse lesions of the cauda equina, however, defæcation has been observed to occur periodically with appropriate

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further relaxation of the sphincter ("automatic defæcation" Müller [27]. and Bálint and Benedict [3]). It is not known whether this is identical with the similar phenomenon observed following transverse lesions of the spinal cord and then associated with evidence of rectal contractility (Head and Riddoch [17].) The precise nature of the reflex activity of the sacral segments in relation to defæcation and to the clinical tone of the sphincter ani is therefore confused and ill-defined.

In the present study we have attempted to define the activity of the rectum and anal sphincter in "automatic defæcation," and to analyse the nervous control of the evacuating mechanism in conditions where spinal reflex activity is present, and in the normal subject.

II.—METHOD.

In each experiment a rubber balloon, which can contain 50 c.c. of air before stretching of the rubber commences, was introduced within the rectum by digital manipulation so that its nearest portion lay over 10 cm. from the anus. Its base was attached by rubber solution to a gum-elastic catheter of 4 mm. outside diameter, sufficiently rigid to prevent its curling within the rectum in the first 10 to 20 cm., and this junction of balloon and catheter was made with the wider distal end of the latter so that occlusion by kinking was less liable to occur (fig. 1B, *d*). This rectal balloon was moderately distended (30 c.c.) to allow its complete unfolding before the experiment commenced. The catheter was attached at its outer end to thick rubber pressure tubing leading to a manometer. A second similar catheter with open end bound to the region of the neck of the balloon (fig. 1B, *e*) is arranged so that fluid may be run from a graduated reservoir into the space between the rectal balloon and the sphincter (fig. 1B, *f*). This space, for convenience of description, we term the "intervening segment." A small glass chamber with fluid level, of the kind used for recording vesical pressures (7), communicated the pressure of this fluid with the air in a second manometric system.

Having experimented with a variety of small balloons attached in various ways to the region of the catheters related to the anal sphincter, we found most satisfactory a balloon mounted on a small brass obturator (fig. 1A, at *a* and B at *g*) in such a way that the upper surface was solid and did not transmit rectal pressure. It was sufficiently rigid to ensure the apposition of the distensible rubber wall to the anal canal with slight bulge above or below when distended, and with narrow (6 mm.) stem to allow the sphincter to close as much as possible when the air space was not distended. The pressure of air within the sphincteric recorder was registered by means of its attachment to thick pressure tubing (fig. 1A, *b*) leading to a third manometer.

The amount of distension of the rectal and sphincteric recording systems was regulated by the introduction of specified amounts of air within the system by means of a syringe. The pressures registered for particular quantities of air injected form the data from which graphs comparing different nervous states are derived. We were aware that the use of air as a medium for pressure registration means that the volumes of air are not absolute, owing to the smaller volume at greater pressures. The volume therefore does not increase in the linear fashion in which the results are graphed. The use of water media and indistensible membranes would be more ideal for volumetric estimations but has disadvantages in the rapid introduction of additional increments of distension. The factors involved in any mathematical representation of the tension at the circumference of an object of increasing circular diameter are of such complexity that we have relied upon the above more simple method, designed only to give some graphic representation to phenomena which can readily be observed and controlled by clinical examination.

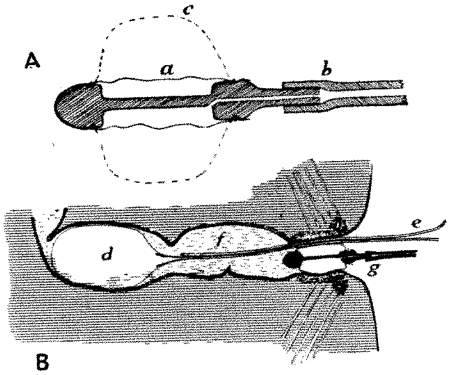


FIG. 1.—Diagrammatic representation of the method of recording used. The sectional diagram A shows the construction of the recorder of pressures in the sphincter ani. A brass core with solid head has a thin rubber membrane *a* attached so that it may be distended by pressure applied through the tubing *b*. The diagrammatic section B shows the rectal balloon *d*, in place, with the additional catheter *e* attached to its neck and communicating with the space *f* ("intervening segment"). The recorder of sphincteric pressure is shown in place at *g*.

Apart from some early experiments the patient lay upon his left side, but we found no distinct difference between the records in this posture and those with the same patient supine. The movements of the abdomen were recorded by balloon applied to the epigastrium beneath a binder.

The manometers used were of glass with thick rubber diaphragm, as used in our earlier work on the bladder [7], and the movements of the membrane recorded photographically by reflected beam of light.

The human rectum is usually stated by anatomists to be 12 to 15 cm. in length, and terminates in the anal canal which is some 2·5 to 3·5 cm. in length. Dr. Hurst informs us that in sigmoidoscopic examination of the living the pelvi-rectal junction lies almost constantly only 11·3 cm. (4½ in.) from the outer extremity of the anal canal. The recorder we have used for the sphincter ani (fig. 1, A) in almost all experiments (where others were used in early experiments, this is mentioned in the text) has an inflatable portion 2·5 cm. in length. Its diameter when inflated until the rubber commences to stretch is 4 cm. Digital examination of the anal canal in cases of cauda equina lesion reveals that the whole canal has sphincteric function, and, as will be related in the text, slow contraction may be observed in the surrounding perineum. The rectal balloon was placed well beyond the sphincteric recorder, and often moved higher during the experiment. Owing to the varying diameter of the rectum we have made no attempt to occlude the passage with the rectal balloon, and fluid run into the intervening segment often ran beyond it in considerable quantities. This rectal balloon, when distended until the rubber just began to stretch, was 4·5 cm. in diameter and 5·5 cm. in length. Distension to greater volumes was not attempted as the less ordinarily suffice to excite contraction of the organ. Distension of a balloon within the lumen of the rectum or anal sphincter acts as a stimulus for a local contraction. It may be objected that the local disturbance excited by the presence of the recorder itself serves to modify the response to other changes. As the relaxations of the sphincter here recorded also could be watched by the observer when the only foreign body within the sphincter was the narrow gum-elastic catheter going to the rectal balloon, we feel certain that in this case this objection cannot hold.

III.—The Effects of Lesions of the Sacral Roots.

It is convenient to consider in each investigation, first the state of the rectum and sphincter, and secondly the relationship obtaining between the two.

Case 1.—H. F., male, aged 46, under the care of the late Dr. Collier. Compression of cauda equina by neurofibroma.

Frequency and urgency of micturition for three years. For two years inability to control bowel evacuation after taking laxatives. Involuntary micturition for two years, readily provoked by coughing and straining for six months. No power of delaying discharge or of interrupting the stream. Bowels very constipated for three months. He stated that he could digitally feel fæces in his rectum, but lacked the power to expel. After taking laxatives evacuation occurred without his knowledge or control. After purgatives this phenomenon was preceded by a sensation of pain in the lower abdomen. Tends to micturate if strains. Twelve months before admission persistent pain over dorsum of foot for two months, and followed by weakness of the left ankle. On examination he showed wasting and weakness of glutei, calf and pretibial muscles, and intrinsic muscles of feet, greater left than right. Marked bulging of perineum on coughing or straining. Knee-jerks very active, right ankle-jerk present, left absent. Abdominal reflexes present. Plantar responses flexor. Anal reflex absent, sphincter relaxed, but not patulous. Deep, but not quite complete loss of sensation to cotton-wool, pin-point and heat and cold over S 3, 4 and 5. Slight loss over S 2. Complete subarachnoid block with Froin's syndrome. Surgical removal of elongated neurofibroma lying among the roots of the cauda equina in the midline and appearing to arise from the filum terminale.

Distension of the rectal balloon in this patient by the sudden introduction of volumes of air up to 50 c.c. evoked evidence of active contractile response. The first 5 c.c. injected brought about a rise of pressure of 23 cm. water, with well-maintained subsequent level (fig. 26, Plate XIV, at *b*). A second 5 c.c. evoked not only a smaller further rise to 27·5 cm. pressure, but a delayed wave of increased pressure (fig. 26, *d*, *e*) which subsided to leave a maintained level of 20 cm. pressure. A further increment of 10 c.c. air added to the balloon now evoked an immediate rise to a peak of 45 cm. water pressure (fig. 26 at *g*) followed by a larger delayed wave of increased pressure, with eventual subsidence to a fresh level of 28 cm. pressure (fig. 26 at *g*, *h*) followed by a series of fluctuations of approximately fifteen seconds' duration. This delayed wave of pressure induced by sudden distension was found to be regularly elicited by sudden distension, and may be likened to the similar "secondary" wave of pressure obtainable from the bladder by sudden stretch of the vesical wall (8).

Distension of the air space of the sphincteric recorder gave rise to a sudden rise of pressure which subsides slowly. When the distension was made in small increments, 1 c.c. at a time at eight seconds' intervals, and the resulting pressures charted in a graph (shown in fig. 12, Plate XII), it will be seen that following the sharp peak of each initial rise of pressure the fall is steeper as the sphincter is further distended. At

5 c.c. (30 c.c. being required to distend the recorder fully to a diameter of 4 cm.), this adaptation of pressure to increased volume is found to vary, being at times rapid, at times non-existent. At this degree of distension of the sphincter slow rounded fluctuations of about ninety seconds' interval were found to be occurring in the state of the sphincter at any constant volume (fig. 27, Plate XIV). The further the sphincter was distended the more obvious these fluctuations became. The adaptation of the sphincter to a suddenly imposed increase of volume of contents appeared steeper when related to the crest of one of the spontaneous fluctuations than when related to the trough. If distension to such a degree were made suddenly by the injection of a single large amount of air into the recorder the pressure rises steeply to a sharp peak and immediately falls to a trough, followed by a reassertion of tone at a slightly higher level (fig. 26 at *a*). This primary relaxation and later reassertion of tone appears identical with the curve published by Gowers [16] of the resistance given to the sudden insertion of an object within the lumen of the sphincter. A momentary increase of abdominal pressure brought about passively by the observer elicits in most striking way a similar relaxation of the sphincter (fig. 27, at *a*). The relaxation here has, however, a delay in onset of over three seconds.

Diminution of the content of the recorder in the sphincter resulted in immediate parallel fall in pressure, but if the lower volume were now kept constant the pressure gradually rose, so that the sphincter maintained an increased grip on the recorder. Movement of the recorder within the sphincter excited no change apart from the fall of pressure when the recorder passed within the rectum or out beyond the sphincter.

Manipulations of the recorder within the sphincter or in volume of the recorder had not the slightest effect on the rectal pressure when that was recorded concurrently. On the other hand, the sphincter was found to be influenced in the most remarkable degree by changes within the rectum. If, the sphincter ani being moderately distended, the rectal balloon were suddenly inflated there ensued a deep relaxation of the pressure exerted by the sphincter ani (fig. 26, Plate XIV, at *c*, *f* and *i*). The relaxation outlasted in duration the induced wave of rectal contraction (fig. 26 at *i*) when that was present, and still occurred when no such wave occurs (fig. 26 at *c*). There is a delay in its onset which suggests that its appearance is related to the onset of the induced rectal contraction wave. A further distension during the trough of this relaxation excited further relaxation, revealing a capacity of the effect to summate.

If fluid were run into the segment of rectum intervening between the rectal balloon and the sphincter recorder ("intervening segment," fig. 1B, *f*) there ensued a rise of rectal pressure of wave form accompanied by a very deep relaxation of the sphincter (fig. 26, Plate XIV, *m*, *n* and fig. 2 at *c*). The slowly developing rise of contraction upon the rectal balloon is clearly not related to any direct mechanical pressure of fluid against the rectal balloon, which was here some 15 cm. within the anus, and is a stimulated contraction in the rectal wall applied to the balloon. The pressure in the fluid in the intervening segment reveals that a more brief and perhaps earlier contraction had occurred in this region of the rectum, and was followed by a further small contraction, *o*, fig. 26, not revealed in the pressure of the higher segment. The same series of events is shown in fig. 2, when the intervening segment is distended by 20 c.c. fluid between *a* and *b*, with resulting wave of rectal pressure at *c* and relaxation of the sphincter ani at *d*. Here the pressure in the intervening segment when the inflow is shut off at *b* reveals a declining wave of pressure. We imagine that the introduction of a small quantity of fluid in this manner subjects a greater area of the rectum to stretch, and thus provokes a greater rectal contraction than does distension of the rectal balloon. Injection of a small quantity of fluid evokes a contraction only of the intervening segment. The mechanism of relaxation of the sphincter in each case appears identical and is related to tension on the wall of the rectum.

As mentioned earlier, the pressure within the sphincter ani underwent long slow fluctuations, and when the rectum was distended there occurred with some of these one or more rectal contractions as at *j*, fig. 26. Such contractions showed a relationship with the relaxation of the sphincter which suggested an opposite, or reciprocal, correspondence between the two, so that spontaneous active contractions of the rectum are accompanied by some corresponding relaxation of the sphincter. This relationship does not hold in inverse manner, for often no rectal contraction accompanies the long slow spontaneous fluctuations in the sphincter (fig. 26, at *p*). The clean-cut relaxation of the sphincter in response to rectal distension is by contrast a transitory phenomenon induced by the phase of increasing tension on the rectal muscle. The period of evacuation will be observed to begin when greatest increase of rectal pressure coincides with greatest relaxation of the sphincter, and declines only as the sphincter closes (fig. 2).

If fluid were run continuously into the intervening segment over a long interval the induced disturbance in the rectum took the form of a series of waves of contraction growing less frequent when the flow is stopped (fig. 2, *e*, *f*, *g*). The sphincter ani relaxed rapidly and maintained a relaxed posture during the whole period of inflow. Fluctuations in this relaxation revealed an intensification of relaxation corresponding to the later half of each rectal wave. This delay in the effect of each rectal wave on the sphincter might be due to an interval of propagation of a wave of contraction downwards from balloon to sphincter, but the pressure in the intervening segment indicates that each wave of contraction tends to involve the whole rectum concurrently (fig. 2, *g*). Evidence of peristaltic contraction in this phenomenon was lacking except for the occasional occurrence of late small waves in the intervening segment as at *o* in fig. 26. That the lack of partition between rectal balloon and intervening segment is not responsible is seen in the independence of the two curves, and is due to the low pressure of the fluid (10 to 20 cm. water pressure).

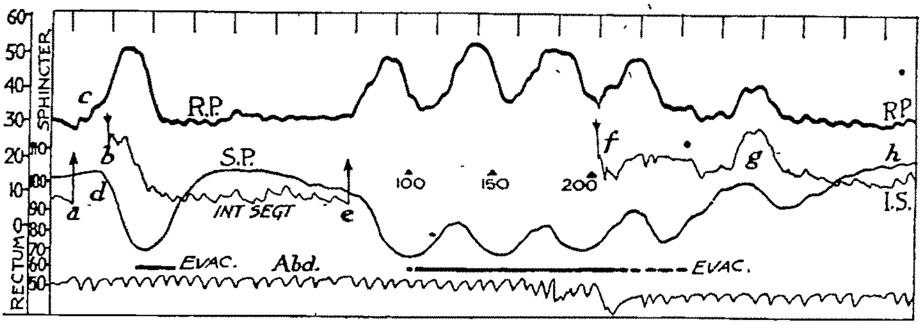


FIG. 2.—To show the effect of distension of the rectum with fluid in Case 1. The tracings in this and all subsequent figures read from left to right. The pressure within the rectal balloon is recorded by the thick line R.P., and the tension in centimetres of water is shown in the first scale. The pressure within the recorder in the sphincter ani is shown in the tracing S.P. The movements of the abdominal wall in the region of the umbilicus is shown in the tracing Abd, where a downward movement represents inspiration. The pressure in the catheter connecting the reservoir with the intervening segment is shown as the thin line INT. SEGT. At *a* 20 c.c. of warm normal saline is allowed to flow from the reservoir into the intervening segment and at *b* the tap to the reservoir is closed. It is again opened from *e* to *f* and 200 c.c run in. Fluid was evacuated past the sphincteric recorder in the intervals indicated by the horizontal black lines (EVAC). Time shown in vertical strokes at 10 second intervals.

The co-ordinated contractions of the rectum and relaxation of the sphincter ani in response to progressive distension of the rectum secured evacuation of fluid past the sphincter as shown in fig. 2. The relationship of this evacuation to the phenomenon of reciprocal contraction indicates that it forms the basis of the automatic defæcation observed in this patient.

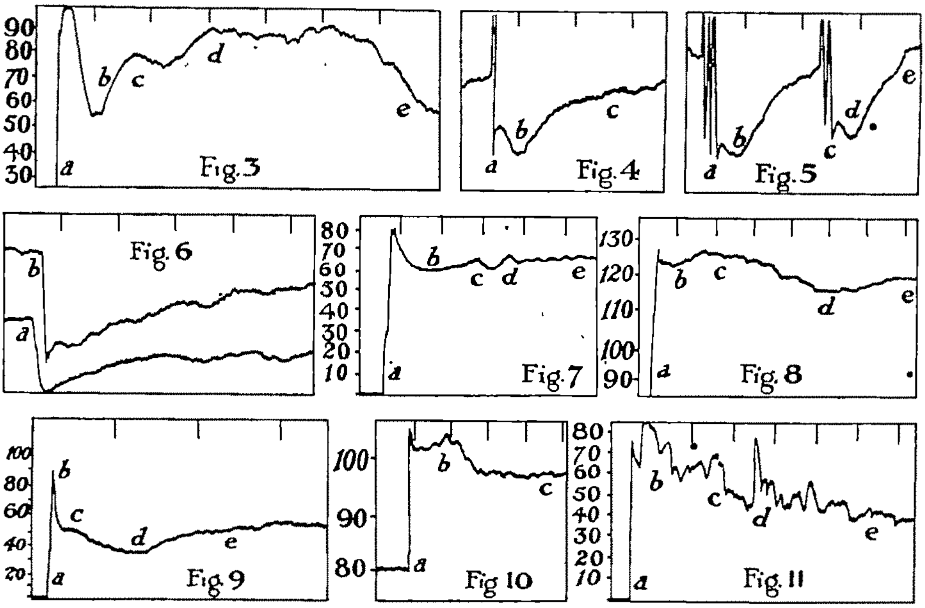
At the time of our examination automatic micturition was well established.

Case 2.—C. R., male, aged 25, under the care of the late Dr. Collier. Spinal arachnoiditis, involving the cauda equina.

Weakness of right foot and leg, with wasting of right leg, for five years. For eighteen months incontinence of urine occurred with exertion. He had to strain to empty his bladder voluntarily. Two years earlier for a period of twelve months he suffered from diarrhœa. Since then evacuation, which he can postpone, has occurred once or twice a day, sometimes easily, usually commenced by straining. On examination he showed slight bulging of lower abdominal muscles on straining. Gross wasting and weakness of glutei, hamstring, calves and intrinsic muscles of feet. Knee-jerks present, ankle-jerks absent. Left lower abdominal absent, others present. Plantar responses absent. Anal reflexes absent. Sphincter patulous. Slight diminution to cotton-wool, pin-point and heat and cold over sacral segments, less over lumbar segments as high as L 2. Partial subarachnoid cerebrospinal fluid block. Laminectomy D 10 to L 3 disclosed thickening of arachnoid, with cystic loculation increasing caudally. Histologically a fragment of arachnoid removed showed only fibrous tissue.

In this patient distension of the rectal balloon, as in Case 1, encountered an immediate resistance (figs. 29, 30) followed by a marked induced "secondary" wave of increased pressure, and succeeded by a moderate degree of plastic adaptation. The secondary wave of pressure was found to be more obvious when the balloon lay some 5 to 10 cm. above the sphincter ani (fig. 30 *g*) than when it lay over 10 cm. above the latter (fig. 30 *a*). This difference is largely one of threshold of stimulus, and even when the balloon was known to be at a high level secondary waves were often obtained by sudden full distension. Spontaneous fluctuations in rectal pressure were not observed.

Distension of the sphincter ani gave rise to an immediate resistance which rapidly melted when further distension ceased, and this fall of pressure was succeeded by a series of small waves of pressure at ten to fifteen seconds' intervals (fig. 3). Distension of the sphincter 1 c.c. at a time revealed low resistance with a high degree of plasticity, as seen in the resulting graph (fig. 13, Plate XII, *a*), and agreeing with its soft patulous feel in digital examination. If the sphincter were examined by gradual distension in this manner its resistance was found to vary not only in brief phases corresponding to its rapid distension or distension of the rectum, but in lasting states of greater relaxation one of which corresponded with distension of the bladder, and another with the appearance of fæcal matter in the upper rectum. The data for the graph recorded in fig. 13*a*, were obtained at a time when reduction in volume of the sphincteric recorder from 20 to 10 c.c. was followed by an immediate drop in pressure with gradual reassertion of a low tonic level after an interval of thirty seconds (fig. 6, *a*). A few minutes later micturition occurred, and the sphincter was then found to be more resistant. Distension by



FIGS. 3-11.—To illustrate the effect of sudden moderate distension of the sphincter ani. Time is shown at the top of each record in vertical strokes at 10 second intervals.

FIG. 3.—From Case 2, to show the effect of the injection of 20 c.c. of air into the sphincter recorder at *a*. The period of injection occupies a little over two seconds. The remainder of the curve shows the reactionary pressure.

FIG. 4.—Also from Case 2. 10 c.c. of air has been injected into the sphincter recorder and a stationary pressure reached. At *a* a further 10 c.c. of air is injected and immediately withdrawn within two seconds. Tensions as in scale of fig. 3.

FIG. 5.—As fig. 4, except that at *a* the manœuvre is repeated three times, and at *c* twice in rapid succession.

FIG. 6.—Also Case 2. At *a* the air within the sphincter recorder, already containing 20 c.c., is reduced to 10 c.c. Later in the experiment, following micturition, the same procedure is repeated and the resulting pressures are shown at *b*. Tensions as fig. 3.

FIG. 7.—From Case 3. At *a* 20 c.c. of air are injected into the previously empty recorder.

FIG. 8.—From Case 9. At *a* 7 c.c. of air were injected into the empty recorder.

FIG. 9.—From Case 5. At *a* 10 c.c. of air were injected into the empty recorder.

FIG. 10.—From a normal subject. At *a* an increment of about 2 c.c. was added to a recorder content of 10 c.c.

FIG. 11.—From a normal subject. The recorder was arranged so that the distensible portion was half extruding from the sphincter. At *a* 10 c.c. of air are introduced suddenly into the recorder.

increments of 1 c.c. now gave data for the graph fig. 13, *b*, and reduction of volume from 20 to 10 c.c. was followed by less reduction of pressure and slow recovery of much higher tone in the ensuing forty seconds (fig. 6, *b*).

The immediate trough of relaxation following a sudden moderate distension of the sphincter in this patient was so well developed (fig. 3 at *b*) that it was examined in further detail. It is not present with small increases in volume, so that the usual interval of eight seconds between observations on distension by small increments allowed sufficient time for a maintained level of pressure to be reached under these circumstances. A transitory small distension, bringing the volume back to the previous level within two seconds, did not reveal any change in existing tone. A brief distension with 10 c.c. of air was followed, however, by a lowering of the existing state of tone, reaching a trough five seconds later, and regaining the previous level in the following twenty to thirty seconds (fig. 4). A momentary stretch of the sphincter therefore induces in it a passing relaxation, and two stretches induce a less deep relaxation than three (fig. 5). The first fall in pressure following upon a sudden and *maintained* stretch is therefore a true relaxation of the sphincture.

Inflation of the rectal balloon brought about relaxation of the tone of the sphincter, as in Case 1, and the relaxation was found to be deeper, but with about the same latency, when the rectal balloon lay within 5 to 7·5 cm. of the sphincter, than when it lay 10 cm. or more above it (fig. 30, *a* and *f*). The presence or absence of a secondary wave of rectal contraction did not modify this reaction. Deflation of the rectal balloon after varying periods of inflation, brought about no change in the sphincter, but movement of the deflated rectal balloon downwards when this could be done without direct disturbance of the sphincter, excited some moderate relaxation of the sphincter (fig. 30, *d*). The effect of momentary brief distension of the rectal balloon revealed that a certain intensity of stimulation was required to effect any relaxation of the sphincter. Single brief distensions were without effect and repeated distension was necessary (fig. 29, *i*, *j*, *k*, *l*, *m*).

Progressive distension of the segment intervening between rectal balloon and sphincter brought about only slight rise of rectal pressure, but was not continued to any large volume. The sphincter in this patient showed when highly tonic the long slow fluctuations also seen in Case 1 (figs. 29, 30), and the effect of moderate progressive distension only lowered the general height of tone, with the appearance of small fluctuations (fig. 28, *g*). There was no voluntary power over the sphincter, and no cutaneous stimulus appeared to affect it. Movement of the sphincteric recorder did not succeed in provoking any effect other than the rise or fall in pressure consistent with its passage into or out of the region of maintained tonic effect and the brief relaxation if the sphincter were thus rapidly distended. Distension of the sphincter, or movement within it, had no effect on the pressure within the rectal balloon.

Accompanying each relaxation of the sphincter induced by rectal distension in this patient not only could the slackening of the skin of the anus be directly observed but also a slow outward movement of the skin of the whole peri-anal region of the perineum. The signalling of the intensity of this relaxation revealed its exact correspondence with the relaxation of the sphincter (fig. 30 at *a*).

This patient had developed only a low grade of automatic micturition, so that small vesical contractions secured enough relaxation of the vesical sphincter to allow evacuation with straining. There was no evidence of function of the external vesical sphincter.

Case 3.—M. R., aged 30, under the care of the late Dr. Collier. Tumour causing compression of cauda equina.

History of severe pain shooting from right buttock, down back of thigh and front of leg to the toes for twenty months; nine months later difficulty in initiating micturition, replaced after three days by precipitant evacuation and incontinence. Desire to pass urine almost continuous, and urethral sensation intact. He experienced desire for defæcation but "did not seem to be able to get it away." After purgation he had difficulty in controlling defæcation. A month later his knees, ankles and feet became weak, and numbness commenced in buttocks, penis and scrotum, backs of calves and feet. On examination he showed slight weakness of flexors of right hip and knee. Knee and ankle jerks present. Abdominal reflexes present. Plantar responses indefinite but tendency to flexion. Anal reflexes absent. Loss of sensation to cotton-wool, pin-point, and heat and cold over sacral skin segments. Almost complete subarachnoid block. The cerebrospinal fluid showed Froin's syndrome. Operative removal of hæmangio-endothelioma from roots of cauda equina.

The reaction of the rectum to sudden moderate increase in the volume of the rectal balloon in this patient was an initial sharp peak of pressure followed by slow and slight adaptation (fig. 31). No induced secondary wave of pressure occurred, unless a very large volume (over 50 c.c.) of increase was made and it was then small. A small secondary wave could be induced by brief pressure on the abdominal wall or by a cough.

Distension of the sphincter ani gave a low pressure curve (fig. 14) with well-marked plastic reaction, and a single moderate distension was followed by a slight following relaxation with recovery (fig. 7, *b*, *c*, *d*) in small rhythmical waves. Movement of the recorder in the sphincter induced a similar following relaxation with recovery.

The effect of distension of the rectal balloon on the sphincter was a definite though not very deep relaxation (fig. 31). More momentary distension of the rectum such as a cough, with associated secondary wave of pressure in the rectum, was also accompanied by a relaxation of the sphincter. The rectal balloon was very low in the rectum, but further insertion of it brought no increase in reaction.

Filling the segment between balloon and sphincter with a small amount of fluid induced a moderate and progressive relaxation of the sphincter with no increase of pressure on the rectal balloon and the intervening segment (fig. 32). Progressive filling of the intervening segment with fluid induced a slow rise of rectal pressure surmounted by a series of irregular small waves, and accompanied by further relaxations of the sphincter, some of which are reciprocal to rectal waves, and each of these with slight delay in onset after the corresponding rectal wave (fig. 33).

This patient showed a contraction of the rectum with each micturition, a phenomenon we had before only observed in reflexly active spinal states [8], and not present in our other cases of cauda equina lesion. Single waves of rectal contraction accompanied spontaneous micturition when the rectum was distended, and relaxation of the sphincter ani was co-ordinated with the rectal contraction (fig. 34). The recovery of tone in the sphincter ani to a supernormal level is here more evident than in other cases, a reflection of the effect of evacuation of fluid both from the bladder and from the intervening segment. Distension of the sphincter or movement within it had no effect of the pressure recorded by the rectal balloon. Distension of the rectum gave rise to a "forcing feeling" vaguely felt in the abdomen, but to no sensation related to the pelvic region. This patient had developed an unusually powerful automatic micturition. There was no evidence of function in the external vesical sphincter.

Case 4.—F. T., aged 28, under the care of Dr. Carmichael. Compression fracture with posterior dislocation of the 11th thoracic vertebra and complete destruction of the spinal cord below the 1st lumbar segment.

Eight months earlier the patient's spine was bent acutely backwards in an accident. There was immediate loss of sensation and power of his legs.

Retention of urine necessitated catheterization: of fæces, enemata. Seven weeks later periodic incontinence of urine and fæces commenced. He presented complete flaccid paraplegia with gross wasting and absent deep reflexes. Abdominal reflexes absent below the 11th dorsal segment. Plantar responses absent. Very slight contraction of the anus could be elicited by a scratch near it. Intermittent spontaneous defæcation when stools were soft. Sphincter usually very patulous. Partial anæsthesia below D 11, complete below L 1. No sensation associated with micturition and defæcation. Sloughing sacral bedsore and perineal fistula. On admission to this hospital he was in a condition of extreme toxæmia from which he succumbed after four weeks. Autopsy revealed complete destruction of all the lumbar and 1st, 2nd, 3rd and 4th sacral segments of the spinal cord. A small piece of intact 5th sacral segment accounted for the anal reflex.

Our observations on this patient were made at the bedside, as his condition did not allow removal to the laboratory. The reaction of the rectum and sphincter to distension was recorded by mercury manometer and the results charted in terms of water pressure for comparison with Cases 1, 2 and 3. The sphincter showed a moderately plastic curve of resistance to distension (fig. 15, *a*), and at the time of examination the sphincter was less patulous than usual. The rectum had maintained a resistance to distension comparable to Cases 1, 2 and 3, but induced waves of rectal pressure were not observed (only slight distension was used). Distension of the rectum was followed by well-defined relaxation of the sphincter ani. Movement within the sphincter evoked no sudden contraction of it. There were slow long fluctuations in the tonic pressure of the sphincter. Some low degree of automaticity of micturition was present but was not closely investigated.

IV.—TRANSVERSE LESIONS RESULTING IN REFLEXLY ACTIVE STATES.

Case 5.—G. R., male, aged 24, under the care of Dr. Carmichael. Fracture dislocation of spine with evidence of destruction of 4th thoracic segment.

Since a motor-cycle accident five months earlier he had been unable to move or feel his lower limbs. There was at first complete retention of urine and fæces. The time of first appearance of active defæcation was not noted. For eight weeks the bladder was emptied by an indwelling catheter. After two and a half months reflex flexion was first observed in the lower limbs, and after a further two weeks active incontinence of urine was observed and the catheterization discontinued. Urine evacuated involuntarily and without his knowledge every ten to fifteen minutes. The intervals had increased and he felt a peculiar feeling in the hypogastrium before evacuation commenced. No power of initiating micturition or defæcation, the latter occurred intermittently without his knowledge or control only after enemata or aperients. On examination he presented complete paralysis of the intercostal muscles below the 4th, and muscles of abdomen and lower limbs. The lower limbs lay in extension, flaccid and wasted. Knee-jerks and right ankle-jerk present, left not elicited. Abdominal reflexes absent, plantar responses extensor with flexor withdrawal of the whole limb. Anal reflexes present. Rectum very distended with soft fæces. There were persistent penile erections. No ejaculation. All forms of sensation lost below the 4th thoracic segment. There was complete cerebrospinal fluid block. X-ray showed fracture of 4th, 5th and 6th thoracic vertebræ, with collapse of 5th thoracic vertebra.

Distension of the rectal balloon in this patient induced a small wave of secondary contraction followed by plastic adaptation to a new tonic level (fig. 35, Plate XV). Even distension to 50 cc. capacity excited but slight rectal secondary contraction. The sphincter ani was moderately resistant to gradual inflation (fig. 16), showing plastic adaptation at an intermediate level. Sudden moderate inflation of it met a high resistance followed by an immediate slight contraction, which was succeeded by a trough of relaxation before steady tonic contraction was reached (fig. 9), and induced a small wave of rectal contraction. Sudden inflation of the rectal balloon induced a relaxation of the sphincter with the usual duration of about twenty seconds (fig. 35). The record of sphincteric contraction showed at times an irregular jerkiness which was due to a very slight irregular contraction of the voluntary musculature of the perineum which was palpable in the region of the external sphincter. A stimulus to the sole of the foot elicited a rapid rise of all pressures with contraction of the levator ani (fig. 37), and when the rectum had been distended this resulted in a late rise of rectal pressure and subsequent evacuation (fig. 37, *b*, *d*).

Distension of the intervening segment resulted in but slight and passive rise of rectal pressure, while the sphincter relaxed moderately and irregularly (fig. 36). For evacuation to occur some additional sudden increase of pressure, such as a passive pressure on the abdominal wall, appeared to be necessary, when the train of events are similar to the effect of stimulation of the sole of the foot. Sudden distension of the sphincter or movement within it was also a stimulus for such evacuation, and both these manœuvres excited an immediate contraction of the sphincter (fig. 38). The rise of pressure in the sphincteric recorder during evacuation at *d* in fig. 37 and *b* in fig. 38 is due to the impaction of passing semi-solid fæcal material against the rubber of the recorder. It will be observed that the waves of pressure in the intervening segment are identical in time with those in the rectum. Owing to the fæcal mass which continuously filled the rectum it was not possible to separate the rectal balloon and sphincter recorder widely.

Digital palpation of the anal sphincter encouraged a moderate tonic resistance, and a brief initial resistance to introduction of the finger was felt to be distinctly related to the outer part of the sphincter. No tonic contraction could be felt in this area. The brief contraction in response to stimulating the sole of the foot occurred in the same part of the sphincter (external sphincter). On continued palpation the sphincter became much softer and evacuation often occurred. Well developed and powerful automatic micturition was present.

Case 6.—H. M., male, aged 24, under the care of Dr. Carmichael. Fracture-dislocation of 1st lumbar vertebra with compression of spinal cord which isolated portions of the sacral segments.

Immediately after a motor-car accident six months earlier he was unable to move either leg, and the left leg felt numb. Sensation and the power of the left leg have remained unaltered, the power of the right leg gradually improved. Spasmodic involuntary flexion of the right knee and adduction at the hip during previous three months. Retention of urine necessitating catheterization for the first six weeks, then frequent involuntary evacuation over which he had no control. For some thirty seconds before micturition occurred he had a feeling of "knotting" in the lower abdomen. No bowel action for six days after the accident. Since then laxatives have secured evacuation following a warning dull ache in the lower abdomen. Constriction of the penis and straining were habitually used to assist defæcation. On examination he showed wasting of the muscles of both lower limbs. Left lower limb completely powerless. No movement at right ankle. Flexion of right knee very weak, extension fair. Extension and abduction and rotation of right thigh almost powerless, flexion and adduction of fair power. Legs lie flaccid and extended. Knee-jerks and ankle-jerks absent. Nocuous stimulation of any part of the skin area of the right sacral segments elicited plantar flexion of toes of both feet, excepting the great toe, in which there was no movement. With this reflex occurred a contraction of the whole perineum, including a faint contraction of the external anal sphincter, more brisk on the left side. Penile erection readily elicited. All forms of sensation lost below the 1st lumbar segment on the left side and the 4th lumbar segment on the right. X-ray revealed fracture dislocation of 1st lumbar vertebra.

Distension of the rectal balloon encountered a slight initial resistance followed by a slow small wave of pressure with slight final adaptation to a well-maintained tonic pressure (fig. 39). The sphincter ani was very resistant to the initial stages of gradual inflation (fig. 17, *a*), but as inflation proceeded the resistance fell, so that the sphincter became very soft and patulous. Evacuation did not at this time occur, but both earlier and immediately subsequent inflation of the sphincter elicited evacuation, and the later fall in the curve is attributed to stimulation of rectal contraction. When a sudden inflation of the sphincter was made the initial high resistance often passed into a very steep fall in pressure in the sphincter in which some jerky contraction heralded a rise of rectal pressure and a large evacuation. At the end of the investigation, when further evacuations of a large quantity of fæcal matter had been induced by other stimuli, the sphincter ani was found to be much more resistant to gradual distension, and the graph of resistance to gradual filling now showed a very steep rise indeed so that the limit of our pressure registration was soon reached (fig. 17, *b*). In view of the large quantity of fæcal material evacuated this heightening of tone of the sphincter may be related to lessening of distension of the pelvic colon as well as of the upper rectum.

Inflation of the rectal balloon brought about a moderate relaxation of the sphincter (fig. 39). Greater inflation of the rectal balloon was followed by deeper and more prolonged relaxation of the sphincter ani. Slight jerky contractions of the external sphincter continued throughout the trough of these relaxations, and do not appear to be affected. On account of loading of the rectum with fæcal matter it was not practicable to investigate the effect of distension of the intervening segment. Spontaneous evacuation was, however, observed, and was preceded by a slow lowering of the tension of the sphincter during which the pressure within the rectum rose only very slightly in the first thirty seconds and mounted gradually into a large wave of high pressure with such force of evacuation of solid fæces as to bring about a rise of pressure in the sphincter recorder. On another occasion a rhythmical series of small waves surmounted the large rise of pressure (fig. 42).

Movement of the recorder within the sphincter, whether inward or by rotation, induced a small peak of increased pressure (figs. 41, 42), which passed into combined rectal contraction and relaxation of the sphincter, and often defæcation. Nocuous stimulation of any part of the cutaneous area of any of the sacral segments on the right side induced a small brisk and brief contraction of the sphincter and levator ani which subsided in three to five seconds, and was often followed at an interval by defæcation (fig. 40, *a*, *b* and *c*).

Digital exploration revealed that the source of the faint jerkiness in the record was faint irregular contraction in the outer segment of the sphincter ani, in that region where the voluntary constriction of the normal sphincter is usually felt. The contraction elicited by cutaneous stimulation of the right sacral segments also caused a faint constriction in this place. Though jerkiness could be felt in this region no distinct tonic constriction could be related to it. The sphincter relaxed slowly and contracted slowly as a whole, and the muscle giving the more rapid contractions felt as if embedded in the outer part of this slowly contracting unit, without giving distinct constriction.

Case 7.—D. McK., aged 28. Fracture dislocation of 11th thoracic vertebra with destruction of 2nd, 3rd, 4th and 5th lumbar segments and partial affection of 11th and 12th dorsal and 1st lumbar segments.

Fourteen months earlier he fell 30 ft. with immediate complete paraplegia. Incontinence of urine developed within a few days. On examination he showed weakness of the abdominal muscles below the umbilicus on both sides. Complete paralysis of lower limbs, with hypotonia, wasting and absent knee-jerks. Both ankle-jerks were present. Stimulation of the skin of the sacral segmental areas induced contraction of the external anal sphincter and levator ani, accompanied by external rotation of the thighs and plantar flexion of the great toes. All sensation lost below the 10th dorsal segment on the left side and 1st lumbar segment on the right side. Lumbar puncture revealed a complete spinal block. He suffered continual constipation. After a purgative or enema he had some warning of imminent defæcation by sense of movement within the abdomen. Any bodily movement then precipitated evacuation. No sensation of passage, and no voluntary control over it.

Distension of the rectum in this patient evoked a high degree of immediate resistance followed by fall to a low tonic level. There was readily obtained an induced wave of rectal contraction (fig. 43), and small series of subsequent waves often occurred. These waves of secondary contractions could also be readily evoked by sudden passive increase of abdominal pressure (fig. 48). The sphincter ani showed the fine jerky irregularities characteristic of slight activity of the voluntary external sphincter. Distension by small increments encountered a moderate resistance (fig. 18). Sudden brief passive abdominal pressure induced a brief contraction in the jerky portion of the sphincter (fig. 48) followed by the slower relaxation of the remainder.

The rectum when well distended showed occasional small waves of contraction at intervals of forty to sixty seconds, each accompanied by a small relaxation in the sphincter commencing at or just before the peak of the rectal wave (fig. 46). In this patient the rectum contracted powerfully with each micturition (reported as Case 5 in our earlier paper on micturition [8]), and with these contractions the anal sphincter relaxes steeply in the later phase of rectal contraction (fig. 47). It will be observed that the pressure in the sphincter rises with the onset of vesical contraction, a phenomenon related to contraction of the whole of the voluntary muscle of the perianal perinium in the early stage of vesical contraction.

This preliminary contraction of the perineum and anal sphincter appeared to be related directly to the rising pressure in the bladder, for when the combined micturition and defæcation were elicited by repeated abdominal pressures the rectal pressure rose early, and passed into a high wave before the similar transition had occurred in the bladder (fig. 49, *b*, *c*), and the sphincter ani showed early relaxation accompanying the first rise of rectal pressure. Here the sphincter ani again contracts before defæcation occurs. The pressure in the sphincter ani was recorded only by means of a small olive-shaped rubber balloon in this patient, so that the wider movements of the involuntary anal sphincter were not clearly differentiated. Well developed reflex micturition was present, with brisk external vesical sphincter.

Case 8.—E. R., male, aged 47, under the care of Dr. Hinds Howell, intramedullary spinal tumour extending from 11th dorsal segment approximately to the level of the 1st sacral segment.

He had had gradually increasing weakness of the lower limbs for a period of eight months, with bouts of aching pain felt in the lumbar spine. Numbness and coldness of the lower limbs had existed for five months, and wasting and twitching of the lower limbs for four months. He had had constipation, and difficulty in initiating micturition for six months. There had been precipitant and uncontrollable defæcation following the administration of aperients. He had complete inability to discriminate between flatus and solid matter. On examination he showed general wasting of the musculature of the lower limbs with flaccid quadriceps and increased tone in the calf muscles. The abdominal reflexes were absent below the 9th dorsal segment. The knee-jerks were diminished, ankle-jerks exaggerated, with ill-sustained ankle clonus. Plantar responses both extensor. Anal reflex present. Almost complete loss of sensation to all forms below the 9th dorsal segment with less deep affection of the 5th lumbar and sacral segments. Sense of position and passive movement deeply impaired in toes, less so in ankle and knee joints. Loss of sense of vibration below 4th lumbar spine. Operative exploration revealed distension of the spinal cord in the region referred to above.

The rectum reacted to distension with the production of secondary waves of moderate size and showed moderate plasticity (fig. 50). The sphincter ani was resistant to inflation and at moderate distension showed slow undulating fluctuations. A single moderate distension evoked, besides the initial resistance, a small peak of contraction related to the outer segment of the sphincter, with subsequent small trough before the maintained tonic level was reached (fig. 50, *a*). The reaction to distension by small increments was not examined, but palpation revealed that apart from the brief initial contraction the sphincter was lax.

Inflation of the rectal balloon evoked a full relaxation of the sphincter ani (as recorded by small olive-shaped balloon) (fig. 50, *c*), while progressive distension of the intervening segment brought about a slow and gradual rise of rectal pressure associated with deep relaxation of the sphincter ani. Although further introduction of fluid ceased the rectal pressure continued to rise, and superimposed smaller fluctuations made their appearance. The resulting large prolonged contraction was accompanied by parallel change in the intervening segment, and secured evacuation of fluid (fig. 51, *c*, *d*, and *e*). The sphincter remained fully relaxed (small olive-shaped recorder), and reverted to a phase of increased tone as the rectal contraction subsided (fig. 51, *f*).

Each involuntary flexor spasm, and flexion induced by stimulation of the sole of the foot, was accompanied by a sharp and brief contraction in the external sphincter (fig. 53, Plate V, *a*, *c*), and often with associated wave of rectal contraction possibly stimulated by perineal movement. The brevity of these reflexly produced contractions suggests their origin in striped muscle, and where the sphincter was already relaxed (fig. 52, *c*, *d*, *e*, *f*) their rapid subsidence left no apparent slower contraction. Each secured brief cessation of evacuation when that was occurring (fig. 52, *c*, *d*). Movement within the sphincter also induced rectal contraction and flickering contraction in the sphincter. Voluntary effort to restrain defæcation was accompanied by rapid but weak and momentary closure of the external sphincter ani not associated with change in the rectal contractions. Where spontaneous contractions of the rectum occurred they had reciprocal relationship to the slow rhythmical fluctuations of tone in the sphincter.

Involuntary powerful micturition with brisk reflex effects had developed in this patient, though he still had some ability to restrain micturition for brief intervals.

Case 9.—H. C., male, aged 60, under the care of Dr. Hinds Howell. Carcinoma of gall-bladder. Secondary deposit compressing spinal cord at level of 5th dorsal segment.

For ten weeks he had aching pains in both groins and indigestion, followed after two weeks by pain in the back. Legs gradually became weaker until six days before admission he was unable to move or to feel his lower limbs. The next day he was unable to pass water and fæces and the next lost all sensation from bowels and bladder. Catheterization was required. Enemata secured small bowel evacuation. He showed on examination complete paralysis of all muscles below the 5th intercostal. Slight extensor rigidity of lower limbs.

Reflexes: brisk knee and ankle-jerks of small range, unsustained ankle clonus. Abdominal reflexes absent. Plantar responses extensor with reflex flexion of lower limbs. Anal reflexes absent. Sphincter ani of moderate tone and plasticity. Sensation completely lost to all forms below the 5th thoracic segment.

In this patient, in whom there was commencing failure of all limb reflexes from general toxæmia at the time of our examination, the reaction of rectum and anal sphincter closely resembled those following cauda equina lesions except that the latter was highly resistant and independent. Distension of the rectum did not elicit any induced wave of contraction although the tonic level was well maintained, and distension of the sphincter encountered a high resistance (fig. 19). At moderate distension the sphincter ani showed long slow fluctuations of pressure (fig. 56), and reacted to rectal distension by only slight relaxation (fig. 56, *d*, *e*). Filling the intervening segment evoked at first deepening of the periodic relaxations of the sphincter without change in pressure in the rectal balloon, and as higher volumes were reached the relaxations of the sphincter deepened, and waves of contraction on the rectal balloon commenced to appear in exact correspondence with each such relaxation (fig. 57, *a*, *b*, *c*, *d*, and *e*). No evacuation occurred, and with further filling the rectal contractions subsided, the relaxation of the sphincter grew less, and a generally lowered tone of the sphincter appeared. Frequent small contractions of the sphincter were now observed (fig. 57, *h-k*). At other times, even with the rectal balloon well distended, there was no evidence of rectal involvement in the rhythmical fluctuation. Distension of the sphincter could excite the appearance of these small rectal waves. No reflex responses in the sphincter were elicited, and movement within the sphincter evoked no rapid contraction.

At the time of this rectal examination the bladder showed no evidence of reaction at any volume up to 1,200 c.c., so that involuntary micturition had failed.

Case 10.—P. C., aged 40, under the care of the late Dr. Collier. Fracture dislocation of 11th thoracic vertebra. Extensive damage to spinal cord from D 7 segment downwards. Residual reflex activity of sacral segments.

In 1915 he fell 38 ft. with immediate loss of power and sensation up to the level of the chest. Retention of urine for two weeks, thereafter incontinence. Power of legs gradually improved and sensation reappeared to some extent on body and right leg. In 1916 retention of urine necessitated catheterization for two to three weeks, after which he gained some ability to pass and control it. Bowels very constipated with precipitant evacuation after taking purgatives. Perforating ulcer and osteomyelitis of left tarsus for eight years. There was slight spasticity of the extensors of both hips and knees. The calf muscles were flaccid. There was wasting of both calves and of both glutei. The abdominal reflexes were present on both sides, the knee-jerks both brisk, the right ankle-jerk present, the left absent. Both plantar responses extensor. Anal reflexes present. There was slight loss of sensation to touch, pain and temperature from D 7 to L 2 segments, and complete loss to all forms over the remaining lumbar and all sacral segments. X-ray revealed a crush fracture of the 1st lumbar vertebræ.

Distension of the rectum resulted in a moderately high rise of pressure followed by a small induced secondary wave (fig. 58), and succeeded by a slight degree of plastic adaptation. Inflation of the sphincteric recorder resulted in a high curve of pressure increase with good adaptation at high distension (fig. 20). The sphincteric record is jerky throughout, and this jerkiness was readily identified with a jerky tonic contraction of the whole voluntary musculature of the perineum. From the rapidity of the contraction and relaxation of each jerk this feature appeared to be directly referable to a slight and flickering tonic contraction of the external voluntary anal sphincter. A cutaneous stimulus to the thigh or sacral skin segments evoked an immediate rapid increase of pressure in the sphincter ani and movement of levator ani. Movement of the recorder within the sphincter, even its rotation through some 19 to 15°, resulted in a similar sudden jerk of contraction in the sphincter and rise of all pressures from contraction of the levator ani.

Distension of the rectal balloon produced a well-defined but small relaxation of the pressure in the sphincter, while distension of the intervening segment evoked well-defined relaxation (fig. 60, *b*) with slow rise of rectal pressure and later powerful and rhythmical fluctuations (fig. 61). These were associated with an earlier rise of pressure in the sphincter (fig. 61 at *d*) and relaxation beginning at or near the crest of each wave of rectal pressure (fig. 61, *e*) coinciding with the onset of evacuation. The same rises occurred with spontaneous rectal contractions, as in fig. 59.

Inflation of the recorder in the sphincter to a moderate volume resulted in a high immediate resistance, followed, after a small "hump," by a trough of relaxation lasting some fifteen seconds. A small wave of rectal contraction often appeared, and then the initial peak was followed by an uninterrupted and more prolonged relaxation (fig. 60, *a*). Insertion of the recorder also elicited a similar contraction of the rectum (fig. 58, *c*).

The bladder reacted briskly to distension and large isolated reflex micturitions could be readily provoked at volumes of 250 to 350 c.c. The external vesical sphincter was active.

Case 11.—E. W., aged 43, under the care of Dr. Hinds Howell. Mildly spastic paraplegia of undetermined cause. Pronounced hypertonia of anal sphincter.

Progressive stiffness, trembling, weakness and coldness of right leg for eight months, and trembling of the left leg for six months before admission. Numbness around the left ankle for three weeks. Right hand shaky, dry and cold for five days. Micturition: for two months urgency and frequency with precipitant evacuation which he is unable to control. If he attempts to pass without first feeling the desire he has to strain. Severe constipation. Urging and straining necessary to get the motion into the back passage and when there it will go no further. So he presses with his finger (between coccyx and anus) and so extrudes the motion. After taking a purgative he feels desire for defæcation continually for about two days, feeling as though the bowel is loaded and should be emptied, but unable to defæcate when this was attempted. Examination revealed optic nystagmus, and impairment of alternating movements of the right upper limb. Weakness of flexion movements of both lower limbs with definite increase in tone of extensors in the right; slight increase in the left. Fibrillation observed in calves. All deep reflexes very active. Abdominal reflexes absent. Plantar responses right extensor with reflex flexion of the limb, left indefinite. Slight loss to all forms of sensation over skin segments S 3, 4 and 5, more definite right than left. Vibration slightly reduced over right malleolus. Right hand colder and drier than left, probably due to vascular causes. The cerebrospinal fluid was normal.

Though the exact nature of the nervous lesion in this patient is obscure he is included in this series on account of his possession of an extreme degree of resistance of the anal sphincter. Inflation of the rectal balloon revealed a high degree of maintained rectal tone, and large secondary waves followed each increment of 10 c.c. beyond 30 c.c. (fig. 63). These secondary waves possibly involved the whole rectum, for they appeared in the intervening segment. With 50 c.c. of air in the rectal balloon slow rhythmical waves occurred at intervals of thirty to fifty seconds. The anal sphincter was extremely resistant to distension (fig. 21), and also showed high degree of recovery of tone with each step of deflation of the sphincter recorder. When the tension within the sphincter passed 50 cm. of water, fluctuation of the pressure appeared, and in continuous record was seen to be due to spontaneous relaxations of the anal sphincter occurring at intervals of sixty to ninety seconds (fig. 63, *c*, *f*). Inflation of the rectum brought about relaxation of the sphincter only when it coincided with the appearance of one of these spontaneous relaxations—which then became immediately deeper. In the intervals the sphincter appeared resistant to this effect (fig. 63, *a*, *d*). Passive increases of abdominal pressure were also without effect (fig. 64, *m*, *o*). Small waves of increase of pressure in the rectal balloon usually accompanied each spontaneous relaxation of the sphincter, and as these increased in size when the rectum became more active the commencement of each was seen to occur some five seconds earlier than the corresponding relaxation of the sphincter.

Progressive filling of the intervening segment with fluid brought about a gradual rise of rectal pressure surmounted by a series of slow contractile waves, and the sphincter ani relaxed more deeply when each of the rhythmical fluctuations became due (fig. 64, *g*, *i*) and at other times more slightly in accompaniment with waves of rectal contraction (fig. 64, *h*, *j*). In spite of increasing rectal distension evacuation occurred only with the first relaxation of the sphincter. Stimulation of the sole of the foot evoked only a brief phasic contraction of the sphincter (fig. 64, *b*, *g*), and any delayed effect was lacking, suggesting that only the external striped sphincter had contracted. Movement of the recorder in or out within the sphincter also evoked this brief contraction without affecting the tone of the involuntary sphincter.

The reaction of the urinary bladder to distension was depressed. A series of small waves of vesical pressure appeared at 400 c.c. and resulted in dribbling micturition. The external vesical sphincter contracted with stimulation of the sole of the foot.

V.—THE NORMAL RECTUM AND ANAL SPHINCTER.

Two normal subjects without history of nervous, vesical or rectal disorder were investigated by the method we have used in the foregoing experiments. As our findings were identical in the two they need not be treated separately.

Distension of the rectal balloon when it lay some 7 to 10 cm. above the anal sphincter, encountered an initial resistance which fell immediately the volume became constant (fig. 65, 66, 70 at *a*). There occurred a small wave of induced rectal contraction, succeeded by a fall to a low maintained tension. When sensation of desire to defæcate was present the secondary induced contraction was found to be present, but not large, and maintained tonic level high (figs. 65, 66). When such desire had been successfully postponed the rectal balloon tended to move inwards to a higher level where tonic contraction was feeble, and the secondary contraction induced by distension was faint or absent. When moved down to proximity to the sphincter, secondary contractions again continued to be elicited, as in fig. 70. Without radiological control we are not certain of the exact anatomical relationship of this inactive region, apart from its lying beyond 15 cm. within the sphincter. With the appearance of an induced wave of contraction the pressure in the intervening segment rises concurrently (fig. 70).

The graphs of resistance of the sphincter ani to distension (figs. 22, *a*, and 23) gave low curves with well-developed plastic adaptation in most of the experiments. As we had hoped to obtain records of the pressures during evacuation of fæces, desire for defæcation was present at the time of distension. Under other circumstances the curve is much higher, so that the later part of the manometer tracing passed beyond our recording paper (fig. 22, *b*). No slow rhythmical fluctuation was observed at any level of distension. The reaction to sudden moderate distension took the form of a sharp peak followed by relaxation, which has a "hump" of late contraction before reaching a maintained level (fig. 10). It is without the high initial resistance of the sphincter of spastic lesions, or the rhythmical later rise of the cauda equina lesions.

The character of the record differs markedly according to the portion of the sphincter ani most related to the recorder. If, for instance, the recorder is moved from within the rectum outwards in a series of steps, the first rise of pressure as intrarectal pressure ceases to be recorded is smooth in general outline, and pulse beats are observed on it (fig. 65, *a* to *b*). When the recorder is moved 1 cm. further out, the pressure rises, but the general characteristics of the curve are the same (fig. 65, *b* to *c*). One cm. further out the rubber portion begins to become visible externally, the pressure rises a little higher, and the tracing presents small irregular jerkings (fig. 65, *c* to *d*). On moving it still further out, the pressure falls slightly (fig. 65, *d* to *e*), and then the record becomes irregular and jerky and requires to be held rigidly to prevent its extrusion (fig. 65, *e* to *f*). The jerkiness is much less obvious if the subject is lying supine, and is then found to become reasserted with any abdominal movement. In the lateral posture it may readily be ascertained by digital examination to be exactly related to the small ring of muscle which contracts during voluntary restraint, the external voluntary sphincter. The small jerky contractions are found to be a tonic contraction of this sphincter, associated with tonic contraction of the pelvic floor in fulfilling the function of tonic regulation of intra-abdominal pressure. Thus the movement of a limb, necessitating some fixation of the trunk, immediately throws the pelvic floor and the external sphincter ani into contraction (fig. 68). It may also be observed that this sphincter, which lies distinctly external to the tonic portion of the sphincter ani, is in general not contracted, though readily thrown into maintained contraction by the synergic movement above mentioned, or by voluntary effort. A sudden moderate distension of the recorder when related to the outer portion of the sphincter ani elicits a large jerk of contraction in the external sphincter, but the subsequent relaxation of the curve is that of the internal sphincter with the superimposed irregular contractions (fig. 11).

Sudden distension of the sphincter or movement within it stimulates a rapid momentary contraction of the levator ani as well as of the external voluntary portion of the sphincter. No contraction of the rectum was observed to be stimulated. Inflation of the rectal balloon, on the other hand, induced a well-defined relaxation of the inner tonic sphincter (fig. 69) in all other respects identical in type with that seen after lesions of the cauda equina. If the sphincter recorder be further out, and registering some jerky contraction of the external sphincter, inflation of the rectal balloon then evokes but faint relaxation (fig. 66, at *a*) attributable to the portion of the recorder still compressed by internal sphincter, while the twitching external sphincter remains unaffected. The relaxation of the internal sphincter produced by a given inflation of the rectal balloon was greater if desire for defæcation were present, and absent if the rectal balloon had moved high in the rectum. The internal anal sphincter is found to show this type of relaxation after an effort to defæcate by straining (fig. 73), and following the sudden rise of abdominal pressure during a cough.

Distension of the intervening segment with a small amount (20 c.c.) of fluid results in rapid and prolonged relaxation of the internal sphincter, and with only slight and mainly passive rise of rectal pressure (fig. 71). If the filling is progressive and the rectal balloon previously inflated, automatic defæcation occurs (fig. 74). The subject is aware of imminent defæcation, and if he does not influence it by straining, a series of large waves of rectal pressure, with small relaxations of the sphincter accompanying them, occurs (fig. 74). These relaxations show reciprocal relationship with the rectal contractions. The jerky external sphincter continues irregular twitching throughout the relaxation. An occasional larger involuntary twitch of the perineum is superimposed as at *b*, fig. 74.

Voluntary restraint of evacuation was seen as an abrupt contraction of the external sphincter. On one occasion, shown in fig. 75, the rectal contraction subsided during the onset of voluntary contraction of the external sphincter, and following cessation of the restraining effect there was very little further evacuation and no further rectal contraction. The wave shown here was the last of a series of such waves evoked by distension, identical in shape with the others, and the rectum had been emptied by the evacuation, so that we do not believe that it has been unduly curtailed. Even when the effort was prolonged for some thirty seconds, there was never observed any direct damping of the rectal contractions, which would subside gradually after continuing for a considerable period. They subside in similar fashion if the rectal contractions are not sufficiently strong to overcome the obstruction of the sphincter by the recorder. Voluntary restraint is also without effect on the internal sphincter, for immediately a restraint is relaxed the tone of the internal sphincter is found to have continued its activity before the restraint (as in fig. 74 at *g*). Voluntary effort to defæcate without abdominal contraction was completely without effect on the rectum and internal anal sphincter, even when on one occasion some 250 c.c. of warm fluid had been run into the intervening segment (fig. 76*c*). That this procedure, though bringing no sensation to the subject, was not without some effect was shown by the finding that sudden distension of the rectum now induced an exceedingly brisk contraction of the rectum, and relaxation of the sphincter had become exceedingly brisk, whereas before they had been sluggish.

The solidity of normal fæces renders pressure observations during normal defæcation difficult to obtain. On one occasion spontaneous defæcation after colonic distension was recorded and rectal contractions and relaxations of the sphincter similar to those obtained by filling the intervening segment were seen, but the waves of rectal pressure reached well over 120 cm. and the passage of solid fæces disturbed the placing of the balloon. A brisk terminal contraction of the levator ani is an interesting feature. The passage of flatus is also accompanied by a similar series of events, though the rectal pressures were often very high indeed (over 150 cm.). Waves of rectal contraction were also observed during micturition but were not associated with any relaxation of the sphincter ani.

VI.—THE PERIPHERAL AUTONOMY OF DEFÆCATION FOLLOWING DESTRUCTION OF SACRAL INNERVATION.

Following accident or disease which brings destruction of the 2nd, 3rd and 4th sacral motor roots on both sides all evidence of any capacity of *rapid* contraction or relaxation in the sphincter ani vanishes. The reactions which we have observed and figured in Cases 1, 2, 3, and 4 are extremely slow in both increase and decrease in tension. There is no apparent effect of voluntary effort to relax or contract the sphincter, and stimulation of the skin is without result. The highly sensitive and rapidly contracting external voluntary sphincter is not in functional evidence. Arloing and Chantre [1, 2] and Elliott [9] have described the slowness with which this muscle loses its striation following deprivation of its motor nerve supply. They further find that response to faradic stimulation remains indefinitely after such degeneration. As it is also described that such contraction in response to faradization, having commenced at one point, spreads to the musculature of the whole perineum [9] it appears very likely that this persistent feature is related not to the striped musculature, but to the involuntary muscle and closely related autonomic plexus which is intimately mingled with the fibres of the external sphincter (Roux [32]), and invests the whole pelvic floor. There is no evidence that the external sphincter remains tonic. We have in Case 2 observed in correspondence with relaxation of the anal sphincter, a relaxation of the surrounding pelvic floor with exactly similar slowness of duration. We therefore believe that, while the striped portion of the anal sphincter may be slow to lose histological structure as a result of nerve lesions, it plays no part in the reaction of the sphincter in these cases.

We may conveniently first consider the "tone" of the non-striped, involuntary anal sphincter, as seen in the cases of lesion of the roots of the cauda equina. Sherrington [35] has defined the general nature of the postural tone of muscle as a reaction to stretch, and pointed the application of this generalization to such phenomena as adaptation of the urinary bladder to the volume of its contents. This property of adaptation in the case of the bladder, originally described by Mosso, we have ourselves observed [7, 8], and found that increasing tension excited increasing contraction of the detrusor musculature, while constant tension excited less contraction. Increase of tension is a more powerful stimulus than constant tension. Following increase in volume an adaptation of posture, with fall of internal pressure, is therefore the direct result of lessening of the stimulating value of stretch. With gradual increase to large volume of vesical content the contractions of the detrusor also tend to fluctuate, and here a further factor of periodic voluntary and involuntary suppression of the vesical reaction occurs and complicates the fundamental postural tonic reaction. Nevertheless at such volumes, and to less degree at smaller volume, a sudden powerful increase in tension is followed by transitory depression of subsequent postural tone, so that tension as a stimulus may have directly opposed effects.

The reaction which the sphincter ani presents, following sudden moderate increase in the volume of its content, takes the form of a sharp initial peak of increased pressure followed by a rapid relaxation to a low pressure for ten to twenty seconds, followed in turn by a gradual rise to a higher level (figs. 3, 7, 26). The later rise usually shows superadded small fluctuations at intervals of five to ten seconds which fade gradually, leaving a residual steadily-maintained pressure, which is the postural tone of the muscle. Immediately the initial resistance is overcome, adaptation to the fresh tension has commenced by a relaxation followed by increase of tone. This form of curve was constantly present in the sphincters of patients with cauda equina lesion, and the early relaxation and later development of tonic contraction are readily palpable on digital exploration of the sphincter. Momentary passive increase of tension induces the same early relaxation although the volume is not changed for more more than two seconds (figs. 4 and 5). These changes, consequent upon distension, may therefore be related directly to a momentary resistance of the involuntary muscle to a sudden stretch, followed by a maintained contraction of the muscle upon its contents. Some small part of this general reaction is certainly due to the purely visco-elastic nature of the tissues concerned, but that the remainder is an expression of active muscular contraction is clearly demonstrated by two further reactions. These are, first the ability of changes at a distance to induce momentary and almost complete relaxation, and secondly the spontaneous and often rhythmical fluctuations in the resistance of the sphincter. Such passing fluctuations form no part of the reaction of non-contractile tissues.

The relationship between the amount of distension of the sphincter and the level of residual maintained contraction and the relationship of this to the degree of initial resistance is illustrated by plotting both these pressures for each 1 c.c. of distension of the recorder. It will be observed (figs. 12 to 15) that both pressures increase with increase in volume of content of the recorder. After a certain degree of distension the adaptation after each increment of distension is such as to maintain the resistance within comparable level over a wide range of distension. Between volumes of 5 and 20 c.c. in our recorder the pressure exerted by the sphincter is largely " plastic " and adaptive. From case to case wide differences are seen, so that this adaptation takes place at a much higher level of pressure in Case 1 than in Case 4 and this higher than in Case 3. Comparable differences in general resistance of the sphincter are seen in the same patient, as in Case 2 (fig. 13, *a* and *b*), here being determined by distension of the urinary bladder. Palpation of the sphincter showed that lowness of the curve reflects that softness of the sphincter commonly called "patulous" (though not actually gaping), and that this condition of resistance is by no means constant in cases of cauda equina lesion.

The reaction of the sphincter ani to sudden distension is, therefore, twofold, an immediate relaxation, and a delayed re-assertion of tonic contraction. The latter is presumably present from the commencement of distension, but at first is overshadowed by the former. There is evidence [34, 6] that the postural tone of striped muscle is an equilibrium between exitation and inhibition, both induced by tension on the muscle, and that when a sudden increase of tension is made the latter predominates, giving rise to the "lengthening reaction." The anal sphincter presents, therefore, a directly comparable reaction, though in the patients here considered the central nervous system does not appear to be concerned. A sudden reduction in content is followed by gradual restitution of tonic contraction at a fresh level of length of muscle fibre (fig. 6) directly comparable to the "shortening reaction" of striped muscle. The posture for the sphincter is determined by tension upon it and stretch is the adequate stimulus for postural "tone."

Sudden inflation of a balloon within the rectum by a small amount of air is accompanied by an immediate rise of pressure within the balloon followed by commencing sharp relaxation to a lower level of maintained contraction. Further sudden increment of volume in the balloon results in further sudden rise of pressure, followed by a slow wave of contraction commencing within two seconds after the distension, so that the eventual resumption of a slightly higher tonic level is delayed. Additional increments in volume excite larger induced waves of rectal contraction. Where the pressure of fluid in the segment intervening between rectal balloon and anal sphincter was recorded as well, it was evident that, apart from slight effects transmitted directly from the balloon to the fluid, the rectal wall of the intervening segment participated directly in these induced waves of pressure upon the rectal balloon when they were large. With small responses only the distended segment showed the contractile wave. There was no evidence of fluctuation travelling towards the anus from the distended region. The residual level of maintained contraction at the level of distension, as in the sphincter ani, increases in proportion to the degree of distension. A segment of the rectum, therefore, reveals a comparable postural relationship to that of the sphincter, except that the phasic disturbance induced by sudden distension begins, not with relaxation, but with a wave of contraction when postural tone is high. The wave of contraction may under these circumstances also be induced with ease by a momentary increase of tension such as a transient pressure through the abdominal wall, and its latency, then more accurately estimated, is found to be 1·2 to 1·8 seconds from the onset of increased tension. Any inhibitory effect derived from stretch of the rectum is not evident, as also is the case in similar waves induced in the urinary bladder [8]. The induced wave of rectal pressure was more readily obtained when the balloon was low in the rectum (*cf.* Case 2), but the movement of the balloon may have altered the condition of the whole rectum. At times the wave was obtained when the balloon was thought to be very high. The maintained level of postural tone in both rectum and anal sphincter presents fluctuations. Some of these are in the form of brief waves at short intervals, and these usually occur when the tonic contraction is settling down to a fresh level following some induced change, as in fig. 26. Others are in the nature of slow fluctuations at long intervals, more commonly seen in the sphincter ani and elicited by full distension. They occur in the sphincter when the rectum is empty, and when the rectal balloon is distended fully the more frequent waves of pressure observed in it are enhanced in size in the phase of relaxation of the fluctuating sphincter. The fluctuations in the sphincter can occur without evidence of parallel changes in rectal pressure.

In 1877, Gowers [15] published a series of observations on the behaviour of the sphincter ani in two cases of transverse lesions of the spinal cord and one complete lesion of the cauda equina. He recorded the contraction of the sphincter in response to insertion of a hollow rubber recorder, and in response to inflation of the rectum with air, and demonstrated the fall in tone of the sphincter after the latter procedure. He found no difference in the two types of lesion, so that it is surprising to find in all the editions of his later book [16] the statement that "if the lumbar centre is inactive there is momentary contraction and then permanent relaxation" of the sphincter in response to its distension. With the later statement we are unable to agree.

Distension of the intervening segment with fluid, the rectal balloon and sphincter recorder being already moderately distended, resulted in the appearance of an isolated rise in rectal pressure, or a premature larger rise if spontaneous fluctuation has been occurring. Immediately the inflow is ceased the pressure within the intervening segment is itself found raised. Later development of the wave in the balloon possibly represents ascending spread of contraction from the locus of distension, as in fig. 26 at *m*, *n* and *o*. Such evidence of progressive contraction is rare, and most usually rhythmical contractions once set up occur contemporaneously in the region of rectal balloon and the fluid in the intervening segment. We have not experimented with two separate balloons, which would perhaps reveal travelling waves of contraction more frequently.

Distension of the rectal balloon induces a deep relaxation of the tone of the sphincter. The presence of a wave of contraction in the rectal segment which is distended is attended by deeper relaxation of the sphincter, but is not essential for its presence. Movement of the balloon within the rectum also induced relaxation of the sphincter, but deflation of the rectal balloon is without any effect. This reaction becomes more striking if a wider area of rectal wall be subjected to tension by the introduction of fluid into the intervening segment. There then ensues a contraction in all segments of the rectum recorded, with deep relaxation of the sphincter, and fluid is evacuated. Continued introduction of fluid results in the appearance of regular fluctuations in rectal pressure with reciprocal relaxations of the sphincter (figs. 2 and 33). Intermittent evacuation may become continuous in the full development of this reciprocal process, by partial fusion of the waves of rectal contraction.

The reciprocal relationship which holds between rectum and anal sphincter is therefore the basis of a mechanism which can secure co-ordinated evacuation. The series of events seen in fig. 2 appear to us adequately to constitute the performance of the automatic co-ordinated and intermittent defæcation readily observed to occur in these patients. The stimulus for its occurrence is distension of the rectum, and sufficient relaxation of the sphincter to allow some passive evacuation of fluid under its own pressure does not occur unless active reciprocal contraction of the rectum provides the driving force of the reaction. For the evacuation of solid fæces more powerful contraction of the rectum would appear necessary. The presence of contraction of the rectum in reponse to distension of the rectal balloon in Case 2, with lack of powerful rectal contraction when the intervening segment was distended, is interpreted as evidence of imperfect and partial development of automatic defæcation.

Automatic defæcation in patients suffering from destruction of the sacral innervation of the rectum appears to be the counterpart of that described in animals where the sacral segments of the spinal cord have been destroyed [14], and also where the more extensive destruction of cord has removed the connection of the rectum and sphincter with the nervous system via the sympathetic nervous system (hypogastric nerves) [27]. The remaining nervous mechanism is that peripheral ganglionic plexus related to the wall of the rectum. The reciprocation between rectum and sphincter which we find to be induced by inflation of a segment of rectum at a distance from the sphincter appears to be of necessity nervous in origin. As with the similar reciprocation observed in the reaction of automatic micturition [8] the nervous mechanism concerned requires a peripheral sensori-motor reaction of reflex kind, foreign to the conception of the sympathetic nervous system as a purely efferent system. That such a peripheral "reflex" is not altogether beyond possibility in relation to parasympathetic ganglia is demonstrated by similar phenomenon of the myenteric reflex in the intestine. In invertebrates smooth muscle without nervous tissue is stated to react to stretch by contraction [4] and propagated waves of contraction are observed in intestine subjected to the action of nicotine [36], so that the postural tone described in the rectum and sphincter cannot with certainty be described as of nervous origin. Nevertheless, the spontaneous concurrent rhythm of fluctuation without phase difference in different parts of the sphincter, and the relaxation of the sphincter brought about by distension of a distant portion of the rectum necessitate the integrating activity of a peripheral nervous plexus.

VII.—The Regulation of Defæcation by the Central Nervous System.

Whether the rectum and sphincter are innervated by the rectovesical plexus alone, or with the addition of reflexly active spinal segments, or in full communication with the whole nervous system, a simple automatic co-ordinated reaction may in them be demonstrated. A rapid increase in the rectal content is followed by a passing fall of tone in the sphincter. A slower but progressive increase of rectal content leads to its actual evacuation of rhythmical contraction of the greater part of the rectum, and more prolonged and rhythmical relaxation of the sphincter.

Both these reactions, of which the first is but a fraction of the second, we have demonstrated in the rectum deprived of sacral innervation, these forming the basis of the clinical phenomenon of "automatic defæcation." Their form when the rectum and sphincter are controlled by the central nervous system appears to have undergone only quantitative change; the mechanism of these reactions still may be regarded as local. The integrity of the spinal and central pathways, though not essential for the performance of elementary automatic defæcation, has nevertheless a certain degree of influence upon it. The approach of the analysis of these effects appears most readily to be made in first considering alterations in the postural tone of the rectum and sphincter, and later the phasic reactions to passing stimuli.

The Postural Tone of the Sphincter Ani and Rectum.

Digital palpation of the sphincter ani evokes a much greater initial resistance in cases with intact sacral innervation than where a lesion of the cauda equina has destroyed this innervation. Such examination is imitated by a sudden moderate distension of the sphincter recorder, and the additional resistance of the former cases is seen in such records as a high initial peak followed by a "hump"-shaped initial delay in relaxation (figs. 8, 9 and 10). The high initial resistance is here, by digital exploration, readily identified with the presence of momentary contraction of the external voluntary sphincter in response to movement within the anus (figs. 38 and 65). When this initial brief resistance is passed some delay in further relaxation is appreciable to careful digital examination. It is variable in degree of development and appears to be a slow wave of contraction in the involuntary portion of the sphincter which obscures the earlier portion of a relaxation, which otherwise resembles that observed in cases of cauda equina lesion. This "hump" of delayed contraction was more prominent when associated with a higher curve of reaction to gradual distension (*cf.* Cases 6 and 9). If our surmise that the postural tone of the sphincter is an equilibrium between relaxation and contraction, both induced in the sphincter by tension upon the muscle, be correct, the appearance of the hump of induced contraction in "hypertonic" sphincters may be interpreted as enhancement of the excitatory element. It was observed in the sphincters of cases of cauda equina lesion when highly tonic.

Gradual distension of the sphincter by small increments does not elicit either contraction of the external sphincter or the hump of delayed relaxation, and is therefore a more true measure of the degree of development of postural tone. Comparison of the graphic representation of resistance of the sphincter in states where the sacral segments are reflexly active (Cases 6 to 10, figs. 16 to 21) with those seen after cauda equina or conus lesions (Cases 1 to 5, figs. 12 to 15) reveals no obvious and constant feature of difference in maintained postural tone. The reaction of the sphincter in any one case usually remained within comparable limits for the duration of our experimental investigation, and on the occasions when the same patient was examined on different days. Occasionally we found changes during the experiment which strongly suggest that over periods of several hours fluctuations of state were occurring. The different shapes of curves may therefore over-emphasize transient, but slow, differences. We have found two causes of such variation, the one being distension of the bladder, the other distension of the upper rectum and probably pelvic colon. We have already commented upon the rise in postural tone in the sphincter in Case 2, resulting from relief from distension of the bladder (fig. 13), and the raised tone of the sphincter immediately following evacuation of the rectum may be indicated (figs. 34, 52 and 62). In Case 9 it will be observed that whereas continued inflow of fluid into the intervening segment elicited at first deepening of the relaxations of the sphincter and the appearance of rhythmical contractions of the rectum (fig. 57, *a* to *g*), these changes later subsided and the sphincter adopted a general lowering of tonic contractions. By this time the large volume of fluid injected, the abdominal discomfort of the patient, and gurgling sounds within the abdomen gave evidence of distension of the distal colon. The initial response of automatic defæcation had here given way to a passive state allowing retrograde distension of the colon, associated with a lowered postural tone of the sphincter. The reverse of this change is illustrated in the experiment on Case 6, in whom a soft "patulous" sphincter became extremely resistant following the evacuation of a very large amount of soft fæces (fig. 17, *a* and *b*). The rectum remained still partly distended, even when the sphincter became more resistant, and therefore distension of the pelvic colon might be in part presumed responsible for the earlier low curve. The lowness of the curve in Case 5 is also probably in greater part due to distension of the lower bowel. So also the resistance of the sphincter of the normal subject to distension was sometimes very high when there was no desire for defæcation (fig. 22, *b*). Garry [11] has demonstrated that, in the cat, movement in the pelvic colon evokes relaxation of the rectum and anal sphincters, and that this effect is abolished by section of the pelvic nerves or by a spinal anæsthetic. Such abolition in an acute experiment does not, however, establish the effect as a spinal reflex, and, as has been described above, the cases of cauda equina lesion after subsidence of spinal shock reveal a similar reaction from the upper rectum. In our own experience, laxity of the anal sphincter appears to be the tonic effect of continued colonic distension of moderate degree. The effect is certainly more active in the cases of transection of the spinal cord. The resistance of the internal sphincter therefore reflects the degree of distension of the lower bowel and rectum.

Apart from these transient changes there appears to be a more durable phenomenon to be associated with "hypertonia" of the sphincter. This is an increased resistance of the sphincter to the relaxing effect of sudden rectal distension, reaching greatest development in Cases 9 and 11 (figs. 56 and 63). In Case 11 this tightness of the sphincter had become a leading complaint of the patient. The high curves in both these patients (figs. 19 and 21) might appear to represent therefore not a transient state of evacuation of the distal bowel, but a "hypertonia" of the sphincter persisting in spite of distension of the rectum. Parallel with the lessening of the effect of sudden distension of the rectal balloon upon the sphincter, there was deficiency and delay in the manner in which the sphincter relaxed and the rectum contracted in response to distension of the intervening segment with fluid in these two cases. In Case 9 this can be attributed to the poor reaction of the rectum resulting from failure of the spinal reflexes. In Case 11 good immediate contractions were obtained by sudden distension of the rectum, but without effect on the sphincter, though the reaction to progressive distension was also poor. The obscure character of the spinal lesion in this case, revealing some evidence of intramedullary damage to the conus medullaris, is unsatisfactory for close analysis. We have included it in the present series to demonstrate the extreme example in our experience of hypertonia of the sphincter. Reflex activity in the voluntary musculature in this case was slight, so that it does not appear possible to relate the tonic resistance of the sphincter to undue reflex enhancement. Such a state differs from the others only in degree, for the reaction of the rectum to general distension is poor, while reaction to inflation of one segment remains good. This dissociation resulting from partial degree of recovery has been seen in Case 2, resulting there from a lesion of the cauda equina.

It becomes clear that it is in conditions where the rectum is capable of active contraction, and is distended, that the internal anal sphincter is of low tone, extremely plastic, and soft to digital exploration. In the same cases evacuation of the rectum, of the bladder, or of the pelvic colon, brought about a return of high tone to the anal sphincter; there is then no obvious difference from one type of lesion to another. So also the sphincter of the normal subject may be as patulous as that following complete cauda equina lesion if the subject has desire for defæcation. The tone of the sphincter ani reflects the degree of activity of the rectum at the time of examination, but its essential and particular mechanism remains identical whatever the nervous lesion. The commonly "patulous" sphincter of cases of established transverse spinal and cauda equina lesions is therefore the clinical sign of the dyschezia from which they suffer. The mechanism of the tone of the sphincter is independent of the central nervous system.

The spontaneous fluctuations at long intervals which characterized the high tone of the sphincter ani, as in Cases 1, 9 and 11, had no corresponding rhythm of fluctuation in the rectum until the latter was well distended. If the sphincter were not distended no corresponding rhythm appeared in the rectal balloon even at high pressure. The propagation and reciprocal nature of the dominant rhythm convince us of its nervous origin, and illustrate in our view that that portion of the hæmorrhoidal plexus which governs the sphincter ani here dominates the remainder. Rhythmical contraction of this kind has been observed frequently in the sphincter of the spinal animal in response to the introduction of a foreign body (Goltz [13], Sherrington [33], and Ott [30]).

Although the reaction of the rectum to sudden or progressive distension undergoes notable changes, its tone or maintained reaction to different degrees of distension is within close limits in all cases examined. The presence or absence of spinal reflex activity does not appear to be associated with any change in the postural tone of the rectum.

Spinal Reflex Activity.

In states of high tonic activity of the anal sphincter the reaction to distension of the rectal balloon, believed to be a fraction of "automatic defæcation," is less readily obtained. It might appear to be hampered by an undue tonicity, or heightening of the reaction of the sphincter to distension. We have found the condition to be a reflection of a state of rectal inactivity which appears to be the result of incomplete recovery from the initial effect of the spinal lesion, and not related to the level of the lesion.

On the other hand reflex activity of the sacral segments of the spinal cord brings qualitative additions to automatic defæcation. In the first place the response to gradual progressive distension of the rectum develops more slowly, and takes the form of a more prolonged rise of rectal pressure, surmounted by smaller waves. This larger contraction is accompanied by similar prolonged and deep relaxation of the sphincter ani. This type of response, seen in figs. 51 and 61, often will not develop until some 800 to 1,000 c.c. of fluid have distended the lower colon as well as the rectum, though the lesser grades of distension excite small waves of rectal contraction and corresponding relaxation of the sphincter. The mechanism of rectal contraction here possesses an inertia which delays its commencement but increases its eventual force. This delay in development closely resembles the similar manner in which the bladder of reflexly active spinal states begins to react to a larger volume than that following cauda equina lesion. It would appear that spinal connections mildly checked the local automatic activity up to a point beyond which a reinforcing activity appeared.

Besides this change in the nature of the response it was found that when the rectum was but slightly distended a variety of stimuli were capable of evoking this more massive reaction. Sudden passive increase in intra-abdominal pressure, movement within the sphincter and to a less degree within the rectum, and nocuous stimulation of the skin of the sacral segments were found to be effective as provocative stimuli. The first of these by increase of intra-rectal tension may be regarded as of the same order as increase of rectal content, and reveals that passive stretch is the adequate stimulus to excite the more powerful and integrated defæcation seen in these patients. We regard this co-ordination of defæcation by the spinal segments as "reflex defæcation," and comparable to the spinal co-ordination of "reflex micturition" as we have defined it in the urinary bladder [8]. The definition of this type of rectal response from the less fused contractions of well-developed automatic defæcation resulting from cauda equina lesion is the ability of a very high rise of pressure to emerge slowly at an interval from a previously induced small active contraction without further stimulus, as in figs. 49, 51 and 37. The rectal contractions of the simple automatic defæcation of cauda equina lesions show almost comparable degree of fusion of small waves when well developed (fig. 33) though reaching lower maximal pressures (40 to 60 cm. water) compared with those of "reflex defæcation" (60 to 100 cm. water pressure). We may compare these pressures with those of 100 to 200 cm. water pressure in the rectum in the course of normal defæcation, even of fluid.

A wave of rectal contraction in Cases 1, 2, or 3, once evoked, subsided following cessation of the stimulus, whereas in the presence of

" reflex defæcation " a wave of rectal contraction set up by some stimulus tended, even if small, to progress slowly to full development of the act in spite of early cessation of the stimulus. This " explosive " character appears to require the same type of autogenetic mechanism we have postulated for "reflex micturition" [8]. The necessary pre-existence of active contraction is not so clearly defined in the case of the rectum as in the bladder, but a quantum of rectal distension is certainly necessary and is provided in the period of cumulative effect (fig. 49). It appears possible that the failure of the forceful reaction to filling of the whole rectum in Case 11, in spite of the presence of well-defined reaction to local distension of the rectal balloon, was due to the partial lesion of the sacral segments. The spinal mechanism had, so to speak, retained a general control of the rectum but was unable to effect the transition from automatic evacuation to reflex evacuation.

Stimuli applied to the sacral skin segments facilitate the appearance of this reflex response at a lower volume of distension in the same manner that they facilitate micturition. Their potency increases as the anus is approached, so that movement within the sphincter is more potent than stimulation of the skin near the anus, and the latter in turn more potent than stimulation of the sole of the foot. Well-defined reflex flexion evoked by scratching any area outside the sacral skin segments, such as the anterior surface of the thigh, was in our experience without effect in evoking this reflex facilitation of defæcation unless it produced an associated abdominal contraction which sufficiently increased rectal tension indirectly.

All the stimuli which evoke reflex facilitation of defæcation also evoke momentary sharp contraction of the external anal sphincter, and of the levator ani (" the anal reflex "). This movement is sufficiently short in response to brief stimuli to disclose the absence of any accompanying change in the involuntary internal sphincter (figs. 52 and 64), though if the latter be contracted upon some object in its lumen a relaxation commences, probably due to movement upon the object (fig. 53).

The cases presented illustrate a series of stages of development of automatic and reflex function of defæcation. The reactions of the peripheral plexus are essential to the development of spinal reflex function. On the other hand failure of reflex function from any cause appears to be followed by redevelopment of depression of the peripheral mechanism with later emergence of automatic defæcation. In all these respects, as in the general features of each state, the behaviour of the rectum follows closely that of the detrusor vesicæ. Thus, in the series of cauda equina lesions Case 3 presented the greatest development both of automatic micturition and automatic defæcation, while Case 1 had both functions moderately developed. In Case 2 only small waves of contraction could be evoked in both rectum and bladder, and evacuation from either organ was chiefly by passive pressure past the minor degrees of relaxation which were reciprocated in the sphincters. In the cases when reflex activity was present in the sacral segments parallel development of both was seen in Cases 5, 6, 7, 8 and 10, with partial failure of both in Cases 9 and 11.

In a previous communication upon nervous disturbances of micturition [8] we included concurrent contraction of rectum and bladder when that occurred as a result of distension of the bladder, as a feature of reflex activity of spinal segments. We have now encountered a case (Case 3 of the present series) where this association occurred in conditions where spinal motor influence over the vesico-rectal plexus appears to be entirely lacking. In this patient such contraction of the rectum was accompanied by evacuation from the anal sphincter (fig. 34), as in those patients in whom there was associated reflex defæcation. In Case 7 this phenomenon was investigated in detail and the early reflex contraction of the perineum and external anal sphincter (figs. 47 and 49), commencing with the beginning of rise of vesical pressure, is notable. It was absent in Case 3. Relaxation of both anal sphincters is secondary to the development of rectal contraction. Contraction of the rectum, associated with micturition in Case 3, and in the normal subject, is seen in the form of isolated or poorly fused wave complexes in the rectum. Defæcation in response to distension of the rectum did not in these patients evoke vesical contraction even when the bladder was distended. The reaction of the bladder to distension is therefore associated with concurrent enhancement of the reaction of the rectum to distension by an activity related to the peripheral plexus. Automatic micturition has a peripheral linkage with contraction of the rectum ; a phasic aspect of the effect of vesical distension in lowering the tone of the sphincter ani. In the spinal animal fully recovered from spinal shock the occurrence of defæcation is associated with a suitable posturing of the hind-limbs and tail [33], a possible explanation of the abduction of the human limbs in the course of the "sacral reflex" (which includes the "anal reflex") seen in Case 7 and commented upon in a previous paper [8]. In a personal communication Sir Charles Sherrington has informed us that in the spinal animal micturition, if in progress, is frequently postponed with the appearance of defæcation. The lack of occurrence of micturition in response to distension of the bowel may therefore be due to direct suppression.

We have found reason to suppose that the portion of the peripheral nervous mechanism which regulates the tone of the sphincter may dominate the rhythm of the whole rectum. Each fluctuation in such spontaneous activity has, when well developed, the same time relations as that which is apparently stimulated from the rectum. Each single wave of such reciprocal activity appears to bring contraction of the rectum as a whole, commencing a few seconds before the onset of the corresponding relaxation of the sphincter. This relationship in time is seen when such spontaneous single waves occur in full development, whether the lesion be of the cauda equina (figs. 2, 33 and 34) or above the sacral segments (figs. 45, 46 and 64), and also in the normal subject (fig. 74). Where the external voluntary sphincter is highly active each such single spontaneous contraction is preceded by a brief jerk of contraction in the sphincter (figs. 59, 62 and 74 at *b*). These same patients also exhibit the larger and longer complete reflex defæcation of which these single waves are then but a fractional form. The duration and intensity of the reaction depends on the intensity of stimulus. In the more powerful reaction a preliminary contraction of the perineum, probably also of the levator ani and external sphincter, frequently appears as the first incident in defæcation. Where a combined response of defæcation and micturition was elicited by distension of the bladder in reflexly active states, the rectum being already partly distended, this early contraction of the external sphincter and retraction of the posterior perineum is especially remarkable (*cf.*, figs. 47, 59 and 61) and may overshadow the relaxation of the internal sphincter as in fig. 62. The anterior portion of the perineum has not been found to contract at this time [8] and the earlier relaxation of the external vesical sphincter indicates that the contraction involves this muscle slightly if at all. The internal anal sphincter does not share the early contraction, which is therefore absent following lesion of the cauda equina. Sir Charles Sherrington has informed us that a brief and forcible contraction of the abdominal wall is frequently observed as an early event in defæcation in the spinal dog with high thoracic transection. None of our patients had a sufficiently high level of reflex activity to include movement of the abdominal wall, but it appears likely that the early contraction of the perineum referred to above is part of the movement which reflexly obtains a rise of abdominal pressure at the commencement of the act.

The external anal sphincter, by its rapid contraction, effects the appropriate cessation of defæcation during the phasic spinal flexion reflex, and it appears justifiable to expect more prolonged closure of this sphincter to be an integral part of more persistent spinal reflexes such as those of progression. In the normal subject this sphincter, in close association with activity of the levator ani, has frequent synergic activity in concurrence with the abdominal musculature. An increase of abdominal pressure excites this active closure, except during defæcation, when the automatic process in the rectum and internal sphincter appear reflexly to facilitate its relaxation. It must be insisted, however, that the primary event stimulated by rise of abdominal pressure is contraction of the rectum. The external anal sphincter, therefore, functions in reflex co-ordination as does the striped external vesical sphincter. There is no evidence that it is maintained in closure in the intervals between evacuations. Palpation with the finger gives the impression of a constricted ring at the site of the external sphincter only during an effort to hold, or during a flexion or other reflex which closes it. At other times, and even during effort which secures its contraction in synergy with the abdominal wall, it can be felt to give irregular flickering contractions which feel to be carried in the substance of the tonic involuntary sphincter rather than forming a separate tonic constriction. Apart from brief retractions at the onset and termination of defæcation activity of the levator ani is difficult to define exactly owing to its mobility. It does not appear to have sphincteric function.

Micturition is subject to a central nervous influence of such kind that deep and prolonged depression of function accompanies the onset of the condition of spinal shock. In this condition the internal vesical sphincter presents maintained closure. Such a state is not obvious in the anal sphincter in the same patients, although inactivity of the bowel, with associated tympanites, is a well-known transient phenomenon. We are indebted to the kindness of Mr. Harold Wilson in allowing us to investigate the following case under his care in St. Bartholomew's Hospital at this stage.

Case 12.—Fracture dislocation of spine, spinal cord severed completely at level of 10th dorsal segment. Spinal shock.

H. R., male, aged 60, fell 12 ft. on January 14, and lost all sensation and power of movement below the waist immediately. On admission to hospital the same day there was found a complete flaccid paraplegia with loss of sensation to all forms up to the 9th dorsal segment on the right side, and the 8th on the left. There was retention of urine for which a catheter was tied in. Stimulation of the sole of either foot induced a slow flexion of the great toe on that side, but no other effect. No other reflex response of any kind was elicited below the level of the lesion. The abdomen became very distended the next day and enemata had no result. On January 16, 1 c.c. of pituitrin was injected hypodermically without result, and this was repeated twice on the 17th. On the evening of the latter day there was some evacuation of flatus. On January 18, 1 c.c. pituitrin resulted in one fluid evacuation, and on January 19 there was incontinence of fluid fæces, which became frequent in the following days up to his death on January 25, from bronchopneumonia. Autopsy revealed complete section of the spinal cord at 10th dorsal level by crush fracture of 8th and 9th dorsal vertebræ.

Our investigation of this patient was made at the bedside on January 18, just before the first fluid motion, so that whatever effect may be related to distension by flatus had been in greater part relieved by pituitrin. Stimulation of the sole of the left foot induced slight contraction in the hamstring muscles of that side, but no other effect. Stimulation of the sole of the right foot evoked well-defined plantar flexion of the right great toe with a very slight contraction of the hamstring muscles. There was no anal reflex, and the knee and ankle jerks were lacking. Inflation of the rectal and anal balloons was made by air and syringe as usual and the pressure readings made by mercury manometer. The graph of resistance of the sphincter to gradual distension is shown in fig. 25, where its high resistance is readily observed. To digital palpation the sphincter felt very resistant, and though distension evoked an immediate plastic reaction the high tone was rapidly reasserted if the finger were kept still. Sudden distension of the rectal balloon with amounts up to 50 c.c. evoked a small relaxation of the sphincter (fig. 79) lasting forty seconds. This was not seen with increments of rectal volume below 50 c.c. The pressure within the rectal balloon revealed no contractile activity and was lacking in any plastic adaptation following a sudden distension. The rectum therefore appeared entirely inactive, the small effect of its passive stretch on the sphincter was the only evidence of co-ordinated effect.

We have already observed that the general lowering of postural tone of the sphincter ani is often but a reflection of some degree of activity of the rectum and probably distal colon, depending upon the degree of their distension. Thus in cases of cauda equina lesion the sphincter ani may be moderately resistant if the rectum has been emptied as in Case 1. The moderately high resistance of the sphincter ani in Case 12, during spinal shock, is therefore entirely attributable to inactivity of the rectum and colon. It is in fact the normal tone of the sphincter, fully developed. The direct effect of spinal shock on the postural mechanism of the sphincter is therefore slight at this stage. From the very nature of the relaxing effect of distension of the rectum upon the internal sphincter ani the initial gaping of the sphincter following section of the pelvic nerves or sacral roots in animals is not evidence that the tone of the sphincter is dependent upon the integrity of these nerves, when the rectum may contain hard masses which it cannot dislodge. Still less does the pressure of fluid in the rectum sufficient to pass the sphincter [10] reflect the tone of the latter. Immediately following section of the sacral dorsal roots Merzbacher [25] found the anal sphincter contracted and only on the second day was it relaxed, while Garry [11] states that dilatation following section of the pelvic nerves in animals is "not a constant response." We have not had an opportunity of examining the sphincter in the first hours of spinal shock when the rectum was empty, but the parallelism between the tonic condition we found in Case 12 with that of the vesical sphincter under similar conditions is obvious. The postural mechanism particular to both vesical and rectal involuntary sphincters appears to be briefly if at all subject to spinal shock, and largely independent of the central nervous system. Relaxation of the vesical sphincter awaits the recovery of active contraction of the detrusor. That of the anal sphincter awaits recovery of rectal contraction, and is preserved from absolute closure only by the small relaxing effect of purely passive stretch of the rectal wall.

The effect of spinal shock on the rectum and colon is one of deep depression. We have presented evidence which strongly suggests that the function of automatic defæcation is integrated by the activity of the local nervous plexus. The depression of rectal and vesical function by spinal shock reflects the loss of that central nervous control which allows the correlation of reflex defæcation or micturition. The subsequent recovery of automatic local function is recovery from this depression. The segmental spinal reflexes in skeletal muscle, once recovered from spinal shock, are not affected by a further spinal transection at lower level. We are not aware of any observation on this point in the case of the bladder or rectum. Once reflex function is recovered in these organs, however, failure of the spinal reflexes of the isolated segment engenders a further period of "shock" in the peripheral nervous plexus concerned from which automatic micturition and defæcation emerge if the patient survives. There are here two levels of higher subsidy of reflexes, so to say, compared with one in skeletal reflexes. The permanent depression of automatic function following severance of the afferent sacral roots (Merzbacher [25]) is more complex, and may provisionally be regarded as retention of the dominance of the ventral roots without afferent keys to unlock the chain of reflexes. States of persistent depression from partial lesions of the sensory tracts, as in tabes, or of the conus as in Case 11, appear to require this mode of explanation.

Spinal shock is essentially an affection of reflex nervous function; an extinction of reflexes by raised threshold of neuronal excitability. Its affection of the motor nervous mechanism serving micturition and defæcation is further evidence of the reflex nature of that peripheral function, albeit related to a peripheral ganglionic plexus of apparently identical histological structure to those sympathetic ganglia of known purity of efferent function. The local mechanism of both bladder and rectum appears closely to resemble that of the myenteric plexus.

The Sympathetic Nervous Pathway and the Participation of the Pelvic Colon.

The phenomena of automatic defæcation have striking contrast with those of automatic micturition, which in the normal subject very rapidly vanish when subjected to willed restraint [7]. Voluntary effort to suppress evacuation from either the bladder or the rectum is immediately effective owing to rapid and powerful closure of the external voluntary sphincters. The rectum, however, continues in contraction, and rhythmical waves have been observed to continue for one minute in spite of prolonged effort to overcome them. Vesical contraction, when extremely intense, is difficult to suppress by voluntary efforts, but even small spontaneous fluctuations in rectal pressure appear to be immune to voluntary inhibition. Relaxation of the effort at any stage reveals that the internal sphincter is still relaxed, so that it also is unaffected by the voluntary effort. The reaction of automatic defæcation declines in a manner so gradual as to be comparable to its defeat by mechanical obstruction. This finding confirms the surgical experience of abolition of voluntary control by surgical interruption of the external sphincter, though we do not agree with Matti [24] that the effect on the internal sphincter is other than that reflecting unbridled rectal activity.

Since voluntary control cannot thus be demonstrated in the reactions of the rectum and anal sphincter, it is perhaps superfluous to note that lesions of the cauda equina below the lumbar sympathetic outflow do not leave any willed effect on these organs referable to this pathway of innervation. Investigation of a case of surgical interference with this pathway was of interest, however, to determine the possibility of change in the involuntary mechanism, particularly since it is stated that stimulation of the hypogastric nerves in animals has various effects on the colon, and contraction of the internal anal sphincter. We are indebted to Mr. Corbett, of St. Bartholomew's Hospital, for permission to investigate the following case under his care:—

Case 13.—Megacolon, operative resection of hypogastric nerves (presacral neurectomy).

T. A., male, aged 54, commenced to suffer from pains in the upper abdomen and from constipation five years earlier. Examination revealed stasis in the colon (megacolon). In July, 1934, the condition was verified by exploratory laparotomy and a cystocolic fold was divided, as well as an adhesion between the duodeno-jejunal flexure and the transverse colon. After an interval of freedom from pain, still subject to constipation, he suffered renewed pain in November, 1934, and it was then found that 4½ pints of opaque fluid were necessary to fill the descending colon alone, and 6½ pints to fill the entire colon. When the radiological appearance was watched under the influence of a spinal anæsthetic, the descending colon. and to less extent the remainder of the colon, were seen to begin to contract, returning the enema. Accordingly, on November 9, 1934, portions of the nerves around the inferior mesenteric artery and the adjacent area of aorta were resected at operation. The hypogastric nerves were readily defined, and their interruption beyond question. The patient remained still constipated, though satisfactory evacuation was secured by enemata.

Five weeks after operative resection of the hypogastric nerves our investigation revealed a lower degree of resistance to inflation of the rectum than normal, so that 60 c.c. was required to bring about the level of maintained contraction normally induced by 30 c.c. Small waves of contraction were observed at full inflation (fig. 78). The sphincter ani was normally resistant when inflated by gradual increments (fig. 24), and digital palpation also revealed no abnormality. Inflation of the rectal balloon from 40 to 60 c.c. induced a small phasic relaxation of the sphincter [provoked by inflation from 10 to 20 c.c. in the normal subject] (fig. 77). Distension of the intervening segment brought about a natural relaxation of the anal sphincter and rising, but low, rectal pressure, with a little evacuation in later stages. Stimulation of the sole of the foot induced a brisk contraction of the external anal sphincter. The behaviour of the sphincter and rectum was therefore of normal order, except for a change related to increase in rectal capacity and present before operation. We have ourselves no direct evidence as to this initial change responsible for the condition of megacolon, but in this patient the poverty of relaxing effect on the sphincter ani, even with full distension of the rectum, is in full accord with the findings of Hurst [20] that here there is an achalasia, or affection of relaxation of the sphincter, by reason of damage to the local nervous plexus linking rectum and sphincter.

We found no change in tone of the sphincter and no absolute loss of the interaction between rectum and anal sphincter attributable to complete absence of hypogastric innervation, just as we find, in comparing Case 5 with Cases 6, 7 and 8, no change referable to the inclusion of the sympathetic innervation with the upper spinal segment in the latter cases. In both types of case distension of the upper rectum or colon with fluid varies the excitability of the lower rectum and lowers the tone of the sphincter ani, so that the reservoir organ as a whole has some reciprocal relationship with the sphincter. Learmonth and Rankin [21] have demonstrated that stimulation of the hypogastric (presacral) nerve in man brings about "strong clonic contraction of the sphincter, followed by several weaker clonic contractions." The type of contraction is evidently that peculiar to the sphincter ani and its provocation in this manner does not entitle the statement that "the thoracolumbar outflow provides the motor nerve supply for this muscle" [21] if by "the motor nerve supply" is meant any effect essential to the usual motor functions of the muscle. In the same manner the rectum appears to share the same independence of sympathetic function as is reported of the rest of the bowel [5].

Any hypothesis of lack of balance resulting from the overaction of the remaining pathway when one or other of the sympathetic or parasympathetic nerve supply of the rectum is interrupted is as unsatisfactory in explanation of clinical disorders of defæcation as we have found it in the parallel disturbances of micturition [8]. In the first place clinical disorder of these functions follows surgical interruption of only one of these pathways, the pelvic (sacral) nerve. Secondly, recovery of function following interruption of the pelvic nerve occurs in identical manner whether the remaining innervation be present or not. Sympathetic innervation appears as inessential to these organs as it is for the function of the heart or the salivary glands. We find full agreement with Cannon [5] that it is in emergency function that the sympathetic system has its value to the individual. Garry [12] has made the pertinent suggestion that where an inhibitory effect of section of the sympathetic nervous supply has been demonstrated by increased activity at open operation in animals the operative exposure has itself possibly supplied the state of emergency.

The question whether distant effects, such as the occasional participation of the whole colon in defæcation, as first described by Hurst [18, 19] and since observed by many others, is mediated by any central pathway is beyond the scope of the present investigation. There is no apparent defect in the delivery of fæcal material, either fluid or solid, to the rectum in the class of nervous disturbance we have investigated. McIntosh [22] has described a delay in the passage of a barium meal through the colon in a child suffering from an obscure lesion of the lumbro-sacral spinal cord. From the dilatation of the rectum and pelvic colon it would appear that here the effect of previous dyschezia has produced sufficient accumulation to retard the progress of the barium.

Our method of investigation has not been designed to give evidence of the behaviour of the region of the pelvi-rectal junction (O'Beirne's "sphincter" [29] or "superior rectal valve" of Houston, as defined by Paterson [31]). Although there is here often a change in the folding of the mucosa, both this and the common post-mortem anatomical narrowing suggestive of the presence of a sphincter are inconstant features (Paterson [31], Hurst [20], and Martin and Burden [23]) and there is no distinct change of the nature of the muscular layers. Hurst [20] states that he does not now believe that any sphincter exists at the pelvi-rectal flexure responsible for the radiological and anatomical appearance but considers it a kink produced by the mobility of the pelvic colon. He has observed [19] that colonic movement does not propel fæces beyond this region unless desire for defæcation is about to occur. We have observed that the further our rectal balloon was separated from the sphincter ani the less local contraction occurred in response to its distension and the less relaxation of the anal sphincter. Distension of the distal colon with fluid appears to have a general relaxing effect on the sphincter ani. A similar more phasic reaction has been noted in experiments upon animals, where Garry [11] describes a reflex dilatation of both the rectum and anal sphincter resulting from movement, but not distension, in the pelvic colon. We prefer to regard the pelvic colon as possessing the same motor function as the rectum, but in less degree. Small masses reaching the rectum are not returned to the colon if not excreted, but larger fluid or semi-fluid masses appear to us to be readily returned to the distal colon if defæcation is obstructed. It therefore appears possible that the most distal pelvic colon and the rectum together serve as an evacuating mechanism which, when filled in sufficient degree from above, contracts powerfully upon its contents and expresses them through the sphincter ani. If the external sphincter obstructs the passage the same contraction drives the greater bulk to the reservoir of the distal colon. On this view the region of the pelvi-rectal junction has significance not as sphincter but as a region of transition from a canal reacting to the distension by its contents by rare massive contractions with long quiet intervals, to a canal reacting to increasing pressure by immediate and cumulative contraction. Our evidence relates only to fluids, however, and the retreat of solid fæcal material has no clear supporting observation. Although well-defined branches of the pelvic (sacral) nerve innervate the pelvic and descending colon [37, 26] the mechanism we have outlined has automatic function following impairment of this innervation, at least as far as the upper rectum. The effect observed by Garry [11] was accounted a reflex by him on account of its absence immediately following section of the pelvic nerves. We feel that a period of subsequent observation for its possible eventual recovery from the resulting depression would be desirable.

We have demonstrated that both following a transverse lesion of the spinal cord or cauda equina fully developed automatic defæcation can secure efficient evacuation of fluids, and that this reaction can be elicited from the rectum alone. The defective evacuation of solids resulting from these nervous lesions appears therefore to result not from deficient reaction to distension of the rectum but from lack of sufficient propulsive power in the act. The deficiency is not an absence of peristalsis, which is as little evident in contraction of the rectum in the normal subject as in these patients. It appears to be related to the general force of contraction of the rectum, which is far greater in the normal subject when evacuating both fluids and solids, even when the abdomen is purposely maintained relaxed. Hurst [19] attributes the lack of evacuation resulting from nervous lesions to lack of appropriate abdominal contraction owing to defective sense of rectal distension, and without doubt rises of abdominal pressure would stimulate the rectum and colon to earlier and more complete contraction. We would urge that the force of contraction of the rectum is the primary factor, without which evacuation, even of fluids, is impossible. When this contractile process is lacking, as in recent cauda equina or conus lesions, abdominal contraction is without effect, just as it is without effect in the inactive rectum of primary dyschezia of otherwise healthy people.

Varying degrees of dyschezia result therefore from the different stages of recovery of the local automatic and reflex mechanism of the rectum from the depression following isolation from the remainder of the nervous system. Even with the most complete recovery of these functions efficiency is still lower than in the natural state, so that the familiar clinical picture of dyschezia with solid fæces and intermittent incontinence of liquid stools results.

SUMMARY OF CONCLUSIONS.

(1) Automatic defæcation resulting from destructive lesions of the sacral innervation of the rectum and anus in man has been studied. In it we have found contraction of the rectum with reciprocal relaxation of the anal sphincter.

(2) This reciprocal relationship between rectum and involuntary sphincter is nervous in mechanism. The adequate stimulus is tension upon the wall of the rectum. Passive tension appears sufficient to bring about slight relaxation of the sphincter. Active tension is a more powerful stimulus.

(3) The nervous mechanism for this "reflex" reaction appears to be related solely to the peripheral nervous plexus.

(4) The mechanism is subject to depression by spinal shock for a brief period during which the sphincter ani relaxes only slightly in response to passive distension of the rectum.

(5) Reflex activity of the sacral segments of the spinal cord brings a progressive character and greater fusion to the rectal contractions with consequent more massive and complete response ("reflex defæcation").

(6) Cutaneous stimulation in the skin area of the sacral segments, with maximal effect at the anus, and activity of the bladder, both facilitate the occurrence of reflex defæcation.

(7) The sympathetic nervous supply (hypogastric nerves) to the rectum and anus does not mediate these automatic and reflex responses.

(8) The postural tone of rectum and sphincter ani is a reaction to passive tension of the muscle concerned. In each a rapidly increasing tension causes tonic contraction to give way to phasic contraction, so that tension is also the stimulus for phasic movement.

(9) The mechanism of postural tone of the sphincter ani is local, and probably is related to the peripheral (? intramural) nervous plexus. It is essentially unaffected as a result of transverse spinal lesions, and the changes in the tonicity of the sphincter reflect only the degree of activity of the rectum and possibly the distal colon.

(10) Voluntary control over defæcation extends directly only to the external voluntary sphincter ani.

(11) The external sphincter is not tonic, though it contracts

reflexly in the course of the flexion reflex, and in synergy with the remainder of the abdominal parietes.

(12) The mechanism of defæcation, provided delivery of fæcal material from the colon is adequate, depends primarily upon the reaction of the rectum to distension.

(13) The inefficiency of defæcation resulting from transverse spinal lesions has explanation in the relatively small force of rectal contraction even with ample recovery of automatic or reflex function.

(14) The functions of micturition and defæcation are almost entirely comparable in their reaction to transverse lesions of the cord. Their mechanism is almost identical except for the lack of any potent voluntary inhibitory control over the contractions of the rectum.

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DESCRIPTION OF PLATES.

PLATE XII.

Graphic representation of the pressures within the recorder in the sphincter ani for each cubic centimetre of air introduced when distension was made 1 c.c. at a time at 8 second intervals. The pressure falls during each interval an amount represented by a vertical fall in the graph. The volume of air introduced is plotted in cubic centimetres on the abcissa, the resulting pressure in centimetres of water on the ordinates. The rise of tension resulting when the recorder is inflated in this manner outside the sphincter is shown in fig. 15 *b*. If the recorder were inflated with its centre 10 cm. below the surface of a bath of water the curve is parallel to fig. 15 *b* after the introduction of the first 1 c.c. and 10 cm. higher at each point. Fig. 12 is from Case 1. Figs. 13 *a* and *b* are from Case 2 under different circumstances (see text). Fig. 14 is from Case 3, and fig. 15 *a* from Case 4. Fig. 16 is from Case 5, and fig. 17 *a* and *b* from Case 6 under differing circumstances (see text). Fig. 18 is from Case 7. This recorder was not in use at the time Case 8 was investigated. Fig. 19 is from Case 9.

PLATE XIII.

Graphs obtained as in Plate XII. Fig. 20 is from Case 10. The data corresponding to the region of the broken line were not recorded as the pressures took the image beyond the edge of the recording paper (over 115 cm. water). Fig. 21 is from Case 11. Fig. 22 *a* and *b* are from a normal subject under different circumstances (see text). Fig. 23 is from another normal subject. Fig. 24 is from Case 13 (presacral neurectomy) and fig. 25 is from Case 12 (spinal shock).

PLATE XIV.

All this and subsequent Plates read from left to right. Time is shown by vertical strokes at 10 second intervals at the top of each record. R.P. indicates the pressure within the rectal balloon, S.P. indicates the tracing of pressure within the recorder in the sphincter, and the curve I.S. traces the pressure in the "intervening segment" where recorded. The tracing Abd. records the movement of the abdominal wall (downward for outward movement as in inspiration). The calibration for the rectal and sphincteric pressures is shown with the first record of each case.

Fig. 26.—From Case 1. The sphincteric recorder is inflated suddenly with 5 c.c. of air at *a*. The rectal balloon is suddenly inflated with 5 c.c. of air at *b*, with a further 5 c.c. at *d*, and a further 10 c.c. at *g*. From *l* to *m* 15 c.c. of fluid is run into the "intervening segment," so that the manometer (I.S.) thereafter records the pressure in this region.

Fig. 27. Also from Case 1, to show spontaneous fluctuations in pressure in the sphincter, the rectum not being inflated. At *a* brief passive pressure is applied to the abdomen. Recorder contains 6 c.c.

Fig. 28.—From Case 2. 50 c.c. air in rectal balloon. 10 c.c. air in sphincteric recorder. From *b* to *c* 25 c.c. fluid is run into intervening segment. From *d* to *e* an additional 100 c.c. is run in.

Fig. 29.—From Case 2 as fig. 28, except that at *a* and *e* the rectal balloon is completely deflated, at *b* and *f* suddenly inflated with 50 c.c. air. The rectal balloon is almost completely deflated at *h*, and at *i* and *j* 1 c.c. is rapidly introduced and immediately withdrawn. At *k* and *l* this is repeated with 5 c.c. and from *m* to *o* 5 c.c. are repeatedly introduced and withdrawn in rapid succession, and finally left in.

FIG. 30.—From Case 2, as figs. 28 and 29. At *a* 50 c.c. air is introduced into the rectum. The whole perineum was observed to relax (see text), the density of the small vertical markings record the approximate degree of relaxation of the perineum as observed by eye. The patient moved slightly at *b*. At *c* the rectal balloon was deflated, and at † at *d* was withdrawn 10 cm. until its attachment lay just above the sphincter recorder. At *e* it was reinflated with 50 c.c. air.

FIG. 31.—From Case 3. The sphincter recorder contains 15 c.c. air, the rectal balloon 10 c.c. air. At *a* 40 c.c. air is injected into the rectal balloon.

FIG. 32.—Case 3. The rectal balloon contains 40 c.c., the sphincter recorder 10 c.c. Between *a* and *b* 50 c.c. of fluid is run into the intervening segment. Evacuation past the sphincter occurs in the duration of the thick horizontal line.

FIG. 33.—Forty seconds after fig. 32. Between *a* and *b* 300 c.c. of fluid is allowed to enter the intervening segment. Evacuation is shown by the thick lower horizontal line.

FIG. 34.—As fig. 33. At ↑ spontaneous micturition was observed to commence, and ceased at ↓. Evacuation of fluid past the sphincter ani occurred in the period shown by the duration of the thick horizontal line (EVAC).

PLATE XV.

FIG. 35.—Case 5. The sphincteric recorder contains 10 c.c. air. At *a* the volume of the rectal balloon is suddenly increased from 10 c.c. air to 40 c.c. air.

FIG. 36.—Case 5. The rectal balloon contains 30 c.c. air, the sphincter recorder 4 c.c. Between *a* and *b* 100 c.c. fluid is run into the intervening segment.

FIG. 37.—Case 5. The rectal balloon contains 40 c.c., the sphincter recorder 4 c.c., and the intervening segment 50 c.c. At *a* the sole of the right foot is scratched. Evacuation of semi-solid fæcal material occurs in the duration of the horizontal lines (EVAC), and tends to extrude the recorders.

FIG. 38.—Case 5, as fig. 37. At *a* the sphincter recorder is suddenly distended with a further 4 c.c. air. Evacuation commences as shown and continues.

FIG. 39.—Case 6. 6 c.c. air in sphincter recorder. At *a* 30 c.c. air is injected into the rectal balloon.

FIG. 40.—Case 6. 10 c.c. air in sphincter recorder, 40 c.c. in rectal balloon. At *a*, *b* and *c* scratches were made in the skin at the right side of the anus.

FIG. 41.—Case 6. 50 c.c. air in rectal balloon, 10 c.c. in sphincter recorder. In the duration of the horizontal line at *a*, the recorder was rotated in the sphincter through some 20 to 30 degrees.

FIG. 42.—As fig. 41. At *a* the recorder was moved quickly outwards in the sphincter and then held still.

FIG. 43.—Case 7. Effect of injection of 25 c.c. air into the rectal balloon. The sphincter recorder was here a small balloon without central core, so that rectal pressure is recorded by it in some degree.

FIG. 44.—Case 7. Rectal balloon contains about 40 c.c. Sphincteric recorder, without core, moderately distended. Between *a* and *b* 100 c.c. fluid run into intervening segment. No evacuation.

FIG. 45.—Case 7. Rectal balloon contains 50 c.c. Intervening segment slightly distended. Sphincter recorder moderately distended (with fresh pressure scale). At ↑ the bladder was gradually distended until micturition occurred in the duration of the horizontal line at M. No evacuation from rectum.

FIG. 46.—Case 7. Tensions as fig. 43. 50 c.c. air in rectal balloon. Sphincter moderately distended. Spontaneous waves.

FIG. 47.—Case 7. As fig. 43. In addition to the record of rectal pressure (R.P.) and pressure within the anal sphincter (S.P.) and intervening segment (I.S.) there is also recorded vesical pressure (V.P.). At ↑ the fluid commences to distend the bladder, and at ↓ the inflow is shut off. The resulting micturition occurs in the duration of the double line M, and evacuation from the rectum occurs in the period shown by the thick line (EVAC).

FIG. 48.—As fig. 47. The bladder is partly distended (50 c.c.). A sharp spike, *a*, shows where a brief passive pressure is made upon the abdominal wall.

PLATE XII.

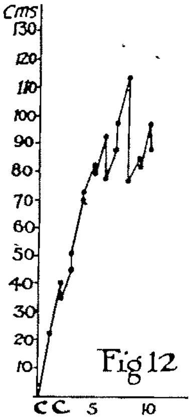
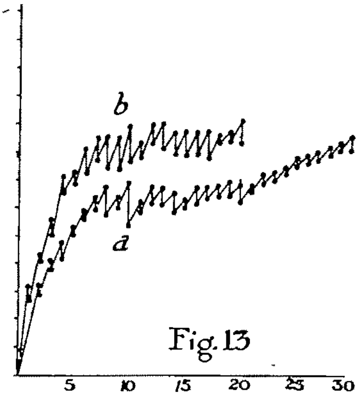


Fig 12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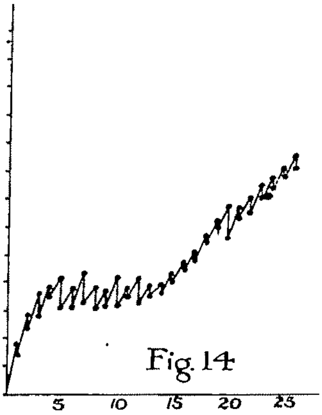
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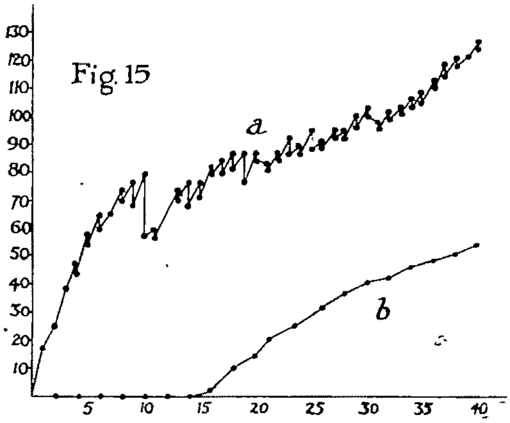
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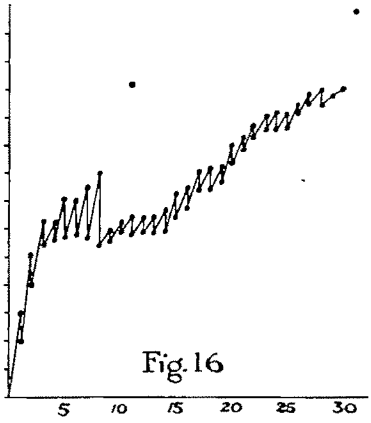
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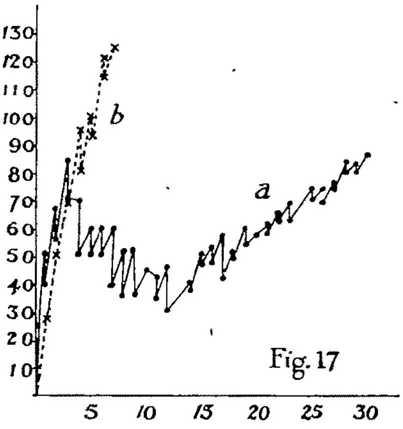
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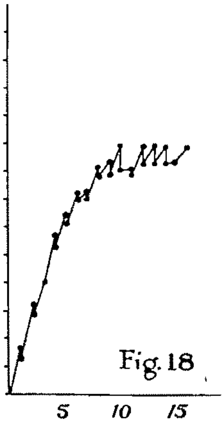
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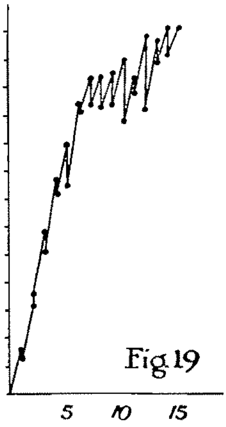
Fig 19

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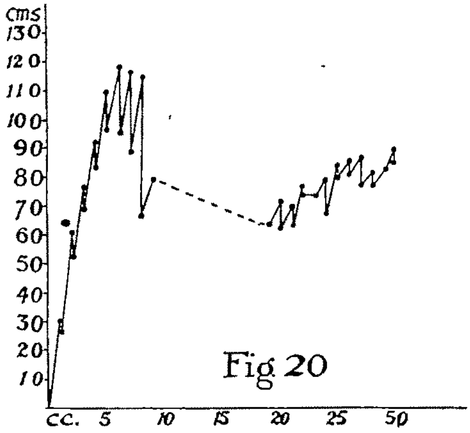
PLATE XIII.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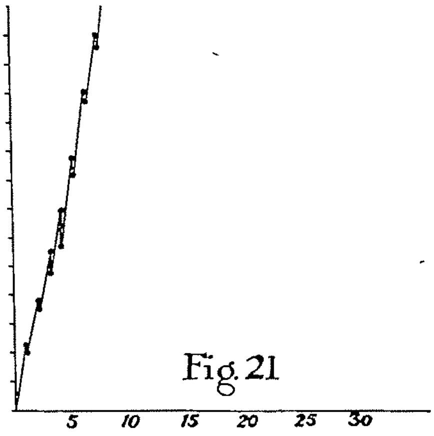
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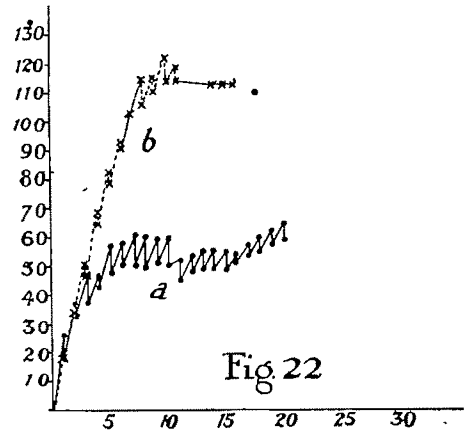
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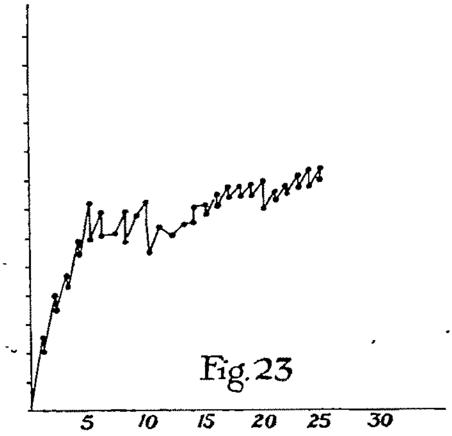
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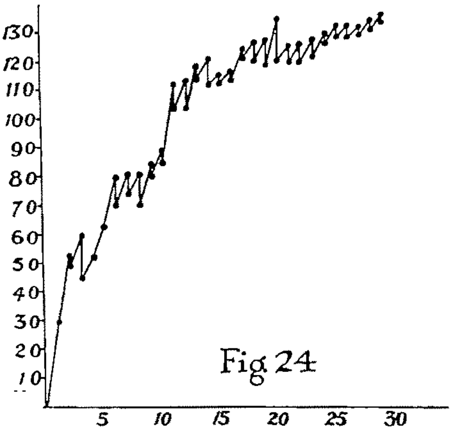
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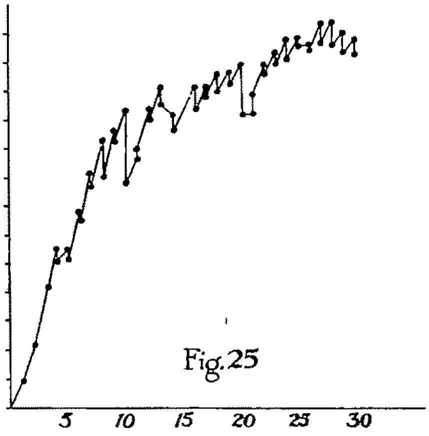
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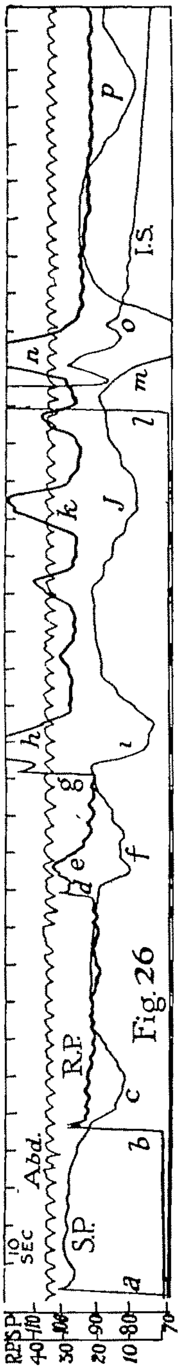
PLATE XIV.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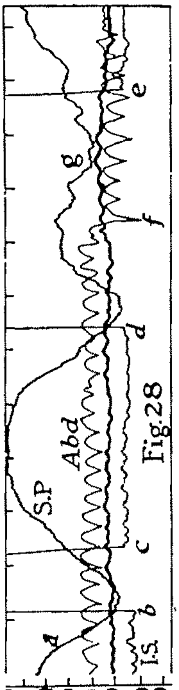
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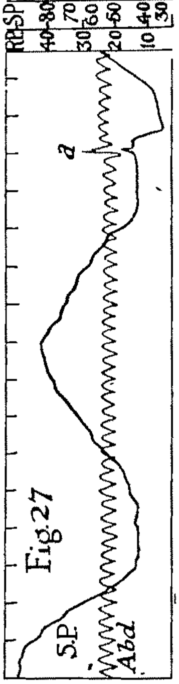
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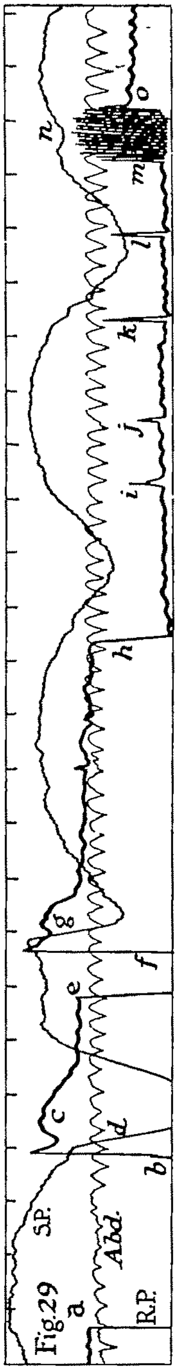
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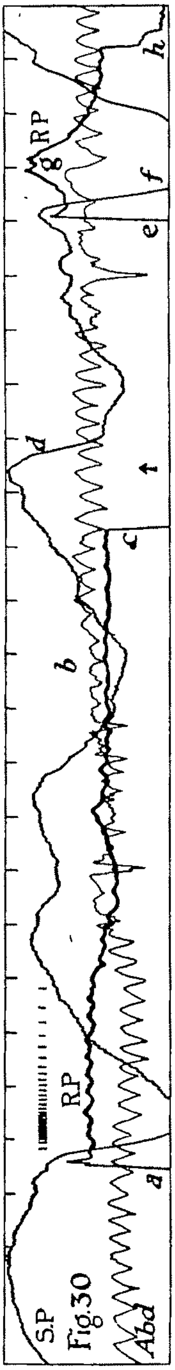
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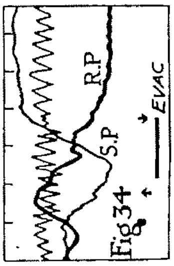
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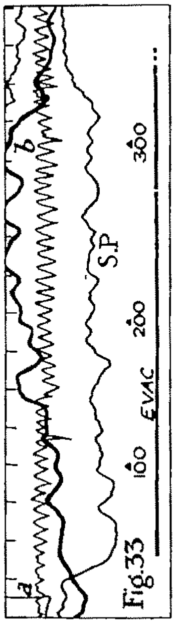
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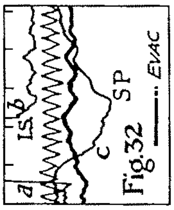
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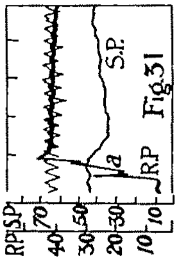
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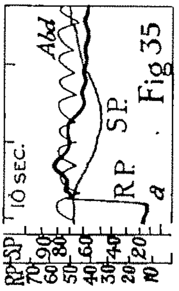
PLATE XV.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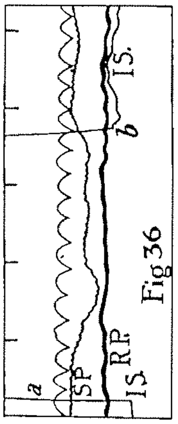
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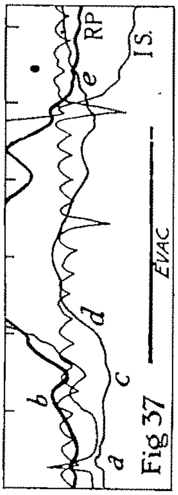
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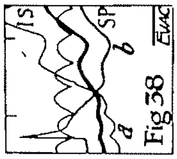
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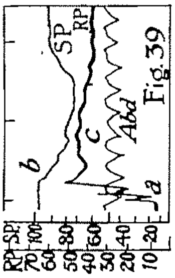
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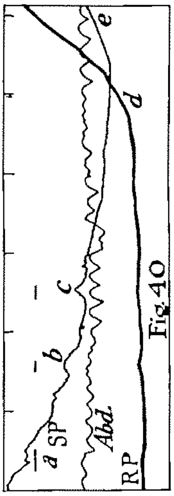
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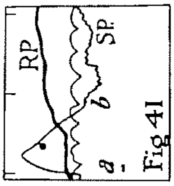
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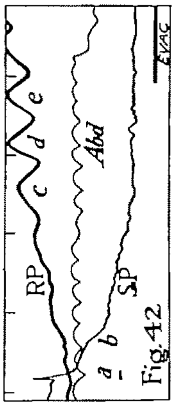
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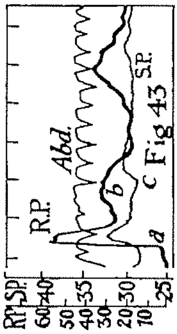
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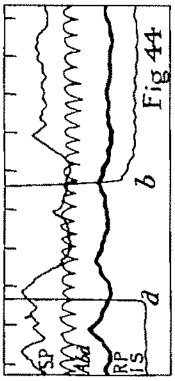
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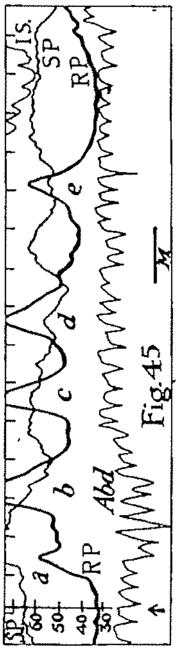
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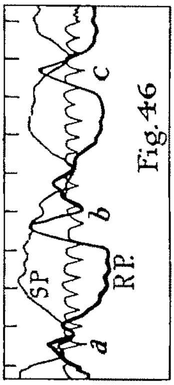
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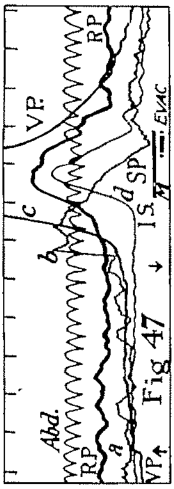
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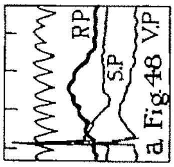
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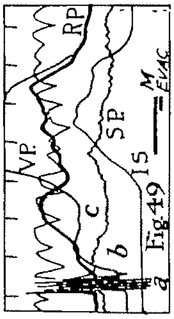
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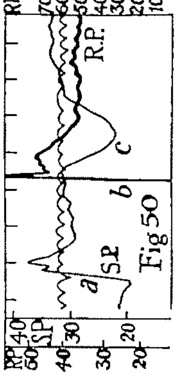
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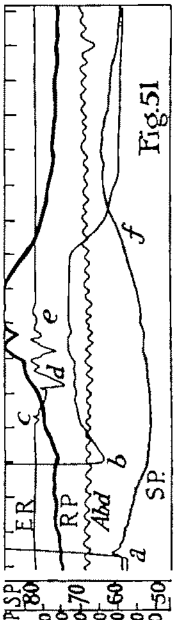
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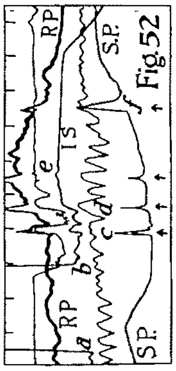
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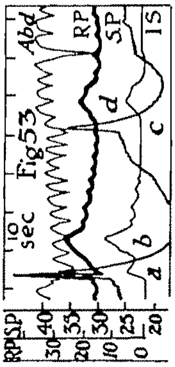

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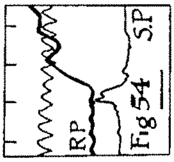

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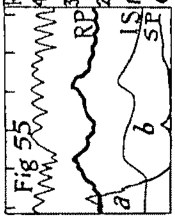

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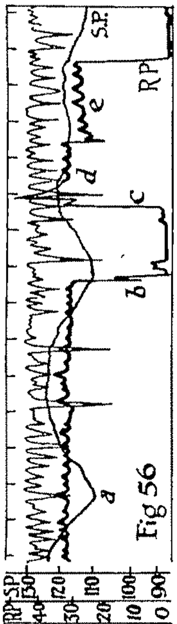

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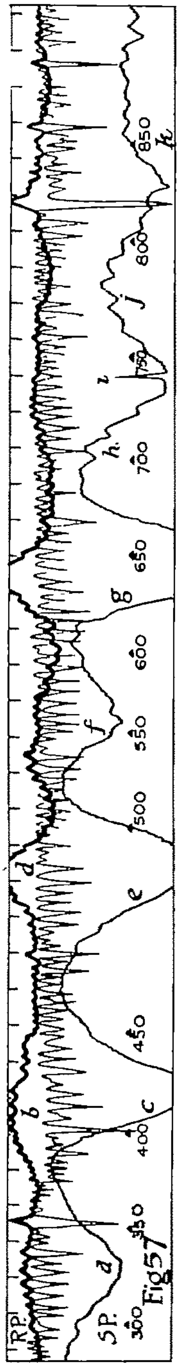

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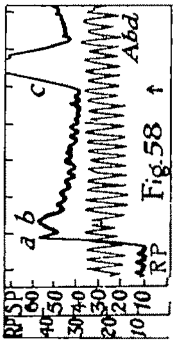

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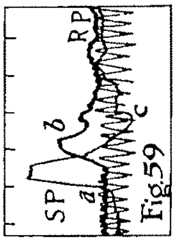

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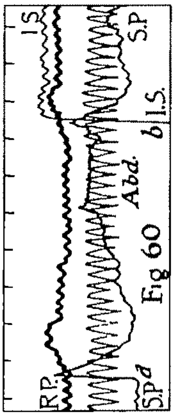

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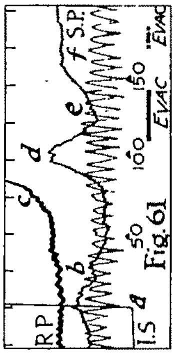

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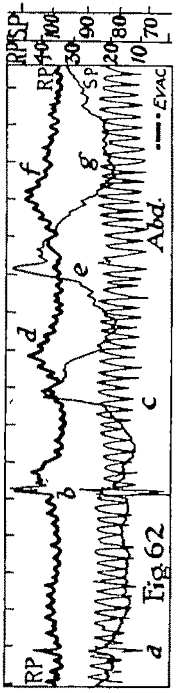

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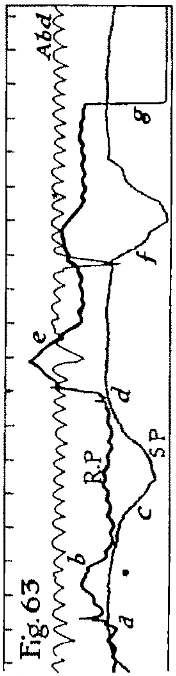

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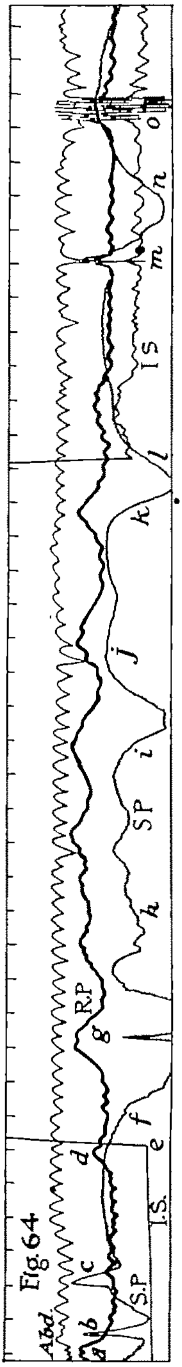

Fig 64

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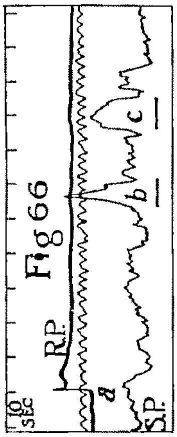
PLATE XVII.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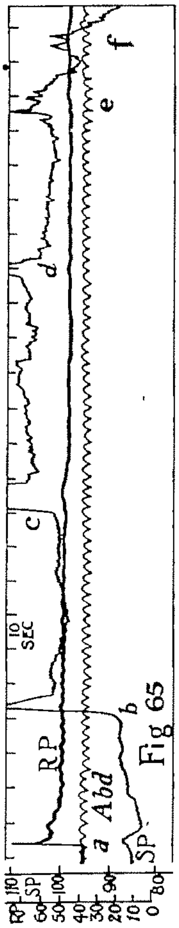
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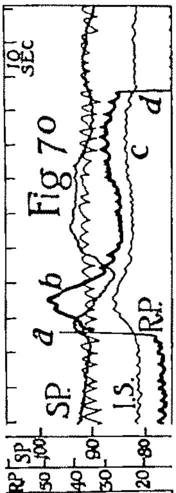
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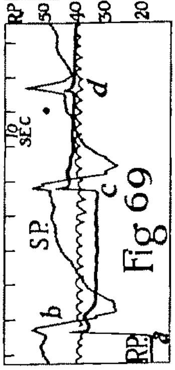
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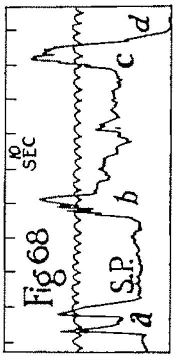
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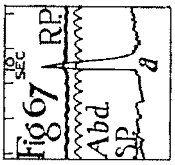
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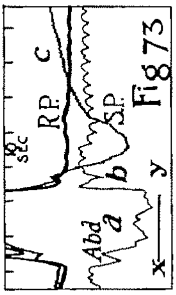
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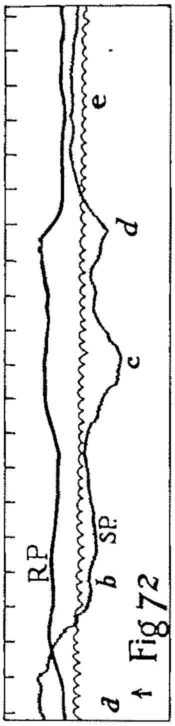
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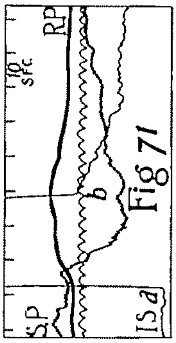
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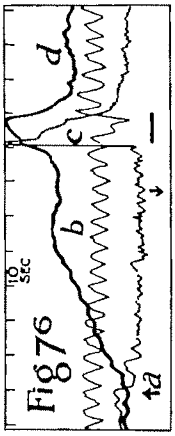
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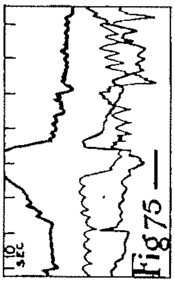
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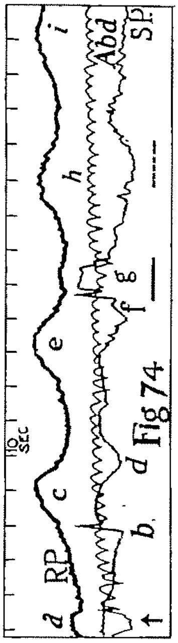
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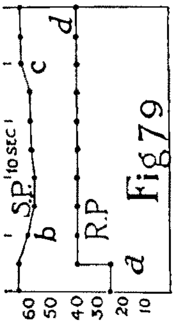
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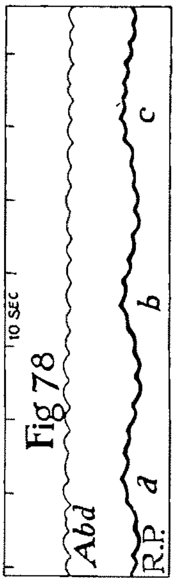
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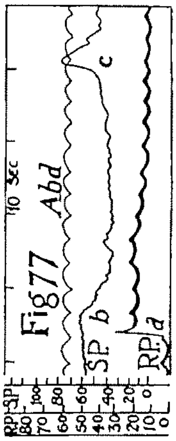
Fig 77

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FIG. 49.—As fig. 47. Effect of repeated passive abdominal pressure at *a*.

FIG. 50.—Case 8. Small coreless balloon used to record pressure in sphincter ani. This was fully distended at *a*. The rectal balloon was distended suddenly with 30 c.c. air at *b*.

FIG. 51.—Case 8. Rectal balloon contained 40 c.c. air. Small coreless balloon in sphincter ani fully distended. Funnel at anus records evacuation of fluid (*c*, *d*, *e*) by downward deflection of tracing, E.R. 50 c.c. fluid is run into the intervening segment between *a* and *b*.

FIG. 52.—Case 8. As fig. 51, except that at the points marked ↑ ↑ ↑ ↑ the outer border of the sole of the right foot was scratched, with resulting brief closure of the sphincter.

PLATE XVI.

FIG. 53.—From Case 8. Rectal balloon contains 30 c.c., sphincteric recorder contains 3 c.c. At *a* a sudden brief passive pressure upon the abdomen elicits a brief contraction of the sphincter followed by a relaxation associated with a wave of rectal contraction, *b*. At *c* a scratch on the inner sole of the left foot elicits a brief contraction of the external sphincter with similar relaxation of the internal sphincter and rectal contraction at *d*.

FIG. 54.—Case 8. As fig. 53. Rectal balloon contains 40 c.c. air, 3 c.c. in balloon in sphincter. In the period shown by a black horizontal line the rectal balloon was pulled gently downwards. A prolonged powerful contraction of the rectum was set up.

FIG. 55.—Case 8. As fig 54. At *a*, and again at *b*, the sphincter recorder was twisted very slightly.

FIG. 56.—Case 9. Rectal balloon contains 20 c.c. Recorder in sphincter 7 c.c. At *a* is seen one of the regular spontaneous fluctuations in pressure in the sphincter. At *b* the rectal balloon is suddenly deflated. At *c* it is suddenly inflated with 20 c.c. air. There is a slight relaxation of the sphincter from *d* to *e*. The rectal balloon is then again deflated.

FIG. 57.—Case 9. As fig. 56. The rectal balloon contains 20 c.c. Fluid was being run gradually into the "intervening segment" and at the commencement of the record 300 c.c. had entered. Between 450 and 500 c.c. the inflow was shut off for twenty seconds, and was then continuous to 850 c.c. when it was shut off (*k*). The sole of the foot was scratched at *i*.

FIG. 58.—Case 10. The rectal balloon contains 30 c.c. air. At *a* an additional 20 c.c. is suddenly added. The wave *b* is due to rectal contraction. At *c* a large wave of rectal contraction occurs in response to digital exploration of the sphincter.

FIG. 59.—Case 10. The rectal balloon contains 50 c.c. air. The sphincter recorder had been slowly distended with 30 c.c. air. At *a* the whole perineum was observed to withdraw spontaneously in the period of high pressure in the sphincter. No evacuation occurred.

FIG. 60.—Case 10. Rectal balloon contains 30 c.c. At *a* the recorder in the sphincter, which contained 2 c.c. air, was suddenly inflated with an additional 8 c.c. At *b* fluid was run into the intervening segment, reaching 50 c.c. at the end of the figure.

FIG. 61.—Case 10. As fig 60. At *a* the inflow of the intervening segment is opened and fluid run in continuously to the end of the figure. Evacuation of fluid past the sphincter occurred in the duration of the thick horizontal lines (EVAC).

FIG. 62.—Case 10. 40 c.c. in rectal balloon. 10 c.c. in sphincter recorder. 100 c.c. fluid in intervening segment. At *a* the patient coughed, at *b* two brief passive pressures on the abdomen. At *c* the perineum was observed to retract suddenly and relax slowly, and again at *e*. Slight evacuation of fluid at end.

FIG. 63.—Case 11. Sphincter recorder contains 4 c.c. Rectal balloon contains 30 c.c. air. At *a* an additional 10 c.c. is suddenly added to the rectal balloon and at *d* an additional 10 c.c. Rectal balloon deflated at *g*. The relaxations of the sphincter at *c* and at *f* are those occurring spontaneously at regular intervals as in fig. 64.

FIG. 64.—Case 11. 40 c.c. air in rectal balloon. 4 c.c. in sphincter recorder. At *a* a spontaneous relaxation of the sphincter briefly interrupted by efforts to contract the perineum voluntarily at *b* and at *c*. At *c* fluid is allowed to distend the intervening segment until 450 c.c. has entered (at *l*). There was no evacuation. At *m* the patient coughed, and at *n* the abdomen was subjected to a series of rapidly repeated pressures.

PLATE XVII.

FIG. 65.—Normal subject. Rectal balloon contains 30 c.c. air, sphincter recorder 10 c.c At *a* an additional 10 c.c. air introduced into rectum. The base of the sphincter recorder was not visible. At *b* the sphincter recorder was withdrawn about 1 cm. At *c*, *d*, *e* and *f* it was withdrawn 1 cm. in each step.

FIG. 66.—Normal subject. Rectal balloon contains 30 c.c. air, sphincter recorder contains 10 c.c. air and is in outer part of sphincter. At *a* an additional 10 c.c. is added to the rectal balloon. At *b* the subject, lying on the left side, extended the right lower limb. At *c* the limb was again flexed.

FIG. 67.—Continuation of fig. 66. At *a* the subject made a brief voluntary contraction of the perineum as if to restrain flatus.

FIG. 68.—Normal subject. As fig. 65. At *a* a brief voluntary restraint. At *b* the sphincter recorder is rapidly moved inwards 2 cm., and again at *c*, passing into the rectum at *d*.

FIG. 69.—Normal subject. Sphincter recorder contains 10 c.c. air and is held in relation to innermost portion of sphincter. At *a* the rectal balloon is suddenly inflated with 30 c.c. air, and at *c* with an additional 10 c.c. At *d* the subject coughed.

FIG. 70.—Normal subject. Sphincter recorder contains 4 c.c. and is related to both parts of the sphincter. At *a* 30 c.c. air is suddenly introduced into the rectal balloon and withdrawn at *d*.

FIG. 71.—Normal subject. 40 c.c. air in rectal balloon, 4 c.c. in sphincter recorder. From *a* to *b* 50 c.c. fluid is run into intervening segment. Tension scale of this figure and also figs. 72 and 73 as in fig. 65.

FIG. 72.—Normal subject. As fig. 71. At † fluid commences to run continuously into the intervening segment until after the end of the figure.

FIG. 73.—One minute after end of fig. 72. In the period *x* to *y* the subject strained ineffectually in attempting to defæcate.

FIG. 74.—Normal subject. Tensions as fig. 70. Rectal balloon contains 40 c.c., sphincter recorder 4 c.c. Fluid is run into the intervening segment from † to end of figure. At *g* the subject attempted to restrain voluntarily for the period of the horizontal line. Some sense of desire for defæcation felt in the period marked by a broken line at *h*.

FIG. 75.—Normal subject. As fig. 74. After long continuing distension of the intervening segment, one of the larger waves of rectal contraction evacuates a large quantity of fluid past the sphincter recorder in the period shown by the horizontal line. The subject then restrained voluntarily, but the rectum was already empty.

FIG. 76.—Normal subject. The rectal balloon contains 40 c.c. At † fluid is run into the intervening segment until the point marked ↓. In the duration of the horizontal line at *c* the subject makes an effort of voluntary restraint.

FIG. 77.—Case 13. Rectal balloon contains 20 c.c. air, sphincter recorder 5 c.c. At *a* an additional 20 c.c. air is added suddenly to the rectal balloon. At *c* the patient involuntarily contracted the perineum.

FIG. 78.—Case 13. Slow rhythmic waves of contraction recorded by the rectal balloon when distended with 40 c.c. air.

FIG. 79.—Case 12. Chart of observed pressures in rectum and sphincter from observations at 5 second intervals at the bedside. Sphincter recorder contained 10 c.c. air. The rectal balloon contained 50 c.c. air, and at *a* an additional 10 c.c. was suddenly added.

A NOTE ON THE DEFINITION OF THE "MOTOR" AND "PREMOTOR" AREAS.

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F. M. R. WALSHE, in a critical survey [18] of a series of papers on the functions of the frontal lobes, recently published from this laboratory, has drawn attention to the fact that in arbitrarily limiting the term " motor area " to the area giganto-pyramidalis of the precentral convolution we have not properly heeded certain earlier neurological teachings, especially those of Hughlings Jackson. His treatment of our work would require no further comment were it not likely seriously to mislead those not intimately acquainted with the field.

I.

Since 1870 [7] the term " motor area " has been used both in neurological and experimental literature as synonymous with the electrically excitable area of the frontal lobes exclusive of the eye field. The work of Campbell [3], Brodmann [1] and others demonstrated in primates that the precentral excitable region was made up of two principal cyto-architectural areas, both evidently motor in function, and designated Area 6 and Area 4 respectively. The term " premotor area " has been introduced within the last ten years to designate the anterior part of the excitable area, but the new term has been used loosely and it has appeared essential to define it more precisely. The simplest and most obvious expedient, as the Vogts [17] and Foerster [5, 6, 7] have frequently pointed out, is to use a terminology that conforms to the principal cyto-architectural fields. After careful consideration of the matter and discussion with investigators in this country and in Europe, we decided a year ago[1] for the purpose of our laboratory publications to restrict the term "premotor area" to the cyto-architectural field designated "Area 6a" (upper part) as outlined by the Vogts and Foerster (see fig. 1). "Area 4" remained for designation, and it seemed entirely appropriate to restrict the term "motor area" to the field of the Betz cells, as had originally been done by Campbell [3] in 1905, and later by von Economo [4, p. 34]. This leaves the useful and non-committal phrase "the excitable area" as a comprehensive term applicable to both regions. The justification for this terminology lies in the fact that cyto-architectural definition has been found useful, and, indeed, indispensable, in considering other areas of discrete function in the cortex. If it is not in harmony with Hughlings Jackson's terminology (whose fundamental conceptions of levels of function are entirely consistent with the subdivision which we have urged), it is scarcely surprising since studies of cyto-architecture had not yet been undertaken in Jackson's time.

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[1] Walshe is quite correct in stating that in some of our earlier papers terms were not adequately defined, and it was our own realization of the fact that caused us to adopt the newer usages [9]. We do not wish to imply that all the corticospinal tracts arise from the motor area, for many writers, most recently Kennard [15] and E. C. Hoff [12], have found that Area 6a contributes extensively to the corticospinal-system, and that the terminal distribution in the cord of these corticospinal fibres differs from the distribution of those from Area 4 [12], which further substantiates the belief that these areas are functionally discrete.

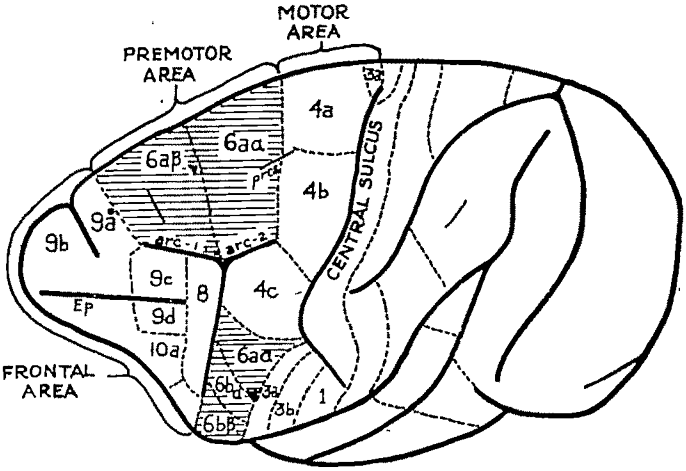

FIG. 1.—The cyto-architectural subdivisions of the frontal lobes of a cercopitheque monkey according to the Vogts [17]. This has formed the basis of Foerster and Penfield's map of the human cortex in which corresponding areas have been identified, and of Fulton and Kennard's studies of the chimpanzee cortex. The excitable cortex includes areas 4, 6 and 8 with their various subdivisions. The motor area is synonymous with area 4, the premotor with area 6a β and 6a α (upper part); areas 6a α (lower part), 6b α and 6b β have not received special designation. The eye field occupies area 8, and the frontal association region areas 9, 10, 11 and 12. Areas 11 and 12, which are on the orbital surface, are not shown on the figure.

II.

Lest any further confusion arise, it is desirable briefly to summarise the observations (on chimpanzees) which Walshe has attempted to elucidate.

(1) *Area* 4.—Complete experimental ablation of Area 4 ("motor area" in our terminology) causes transient paralysis, most marked and enduring in the distal joints, transient depression of reflexes and transient flaccidity. In the stages of recovery from a lesion of Area 4 deep reflexes may become moderately hyperactive, but gross spasticity has never been observed at any age of recovery following lesions sharply restricted to area 4.[1]

(2) *Area* 6a.—Ablation of Area 6a (upper part, "premotor area" of our terminology) at a primary operation, or after removal of Area 4, causes a disorganisation of the more highly integrated voluntary movements [14] producing a state akin to apraxia in man (a term scarcely applicable to animals); and such lesions lead also to the immediate appearance of spasticity with increase of deep reflexes, forced grasping, vasomotor disturbances and certain specific reflex signs such as those of Rossolimo, Mendel-Bechterew, Hoffmann, and the fanning sign of Babinski [16].

(3) *Bilateral ablation of Area* 4 *and* 6a.—Bilateral ablations of motor and premotor areas in mature monkeys causes permanent paralysis of voluntary movements, and the postural reflex state of the skeletal musculature of such a preparation is indistinguishable from that of a thalamic monkey; but if a part of one area, motor or premotor, remains intact in one hemisphere, the animal recovers some degree of voluntary power in all four extremities.

(4) *Areas* 9, 10, 11 *and* 12.—Bilateral ablation of the frontal association areas does not cause forced grasping and gives rise to no other disturbance in reflexes or in motor skill; complex behavioural deficits appear, however, which are beyond the scope of this note and are fully described elsewhere [13, 14, 9, 11].

Walshe's discussion focusses attention upon the possible functional subdivisions of the premotor area, a problem which has been under investigation for several years, but we are not yet in a position to discuss the matter in detail beyond stating that the posterior half (Area 6a α of the Vogts, fig. 1) is more excitable than the anterior part (Area 6a β), and on stimulation yields more discrete movements (Vogts [17], Foerster and Penfield [5, 6], Bucy [2]), and that subtotal extirpation of the premotor area fails to produce forced grasping, i.e. removal of Area

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[1] Prior to December 1932, we were unaware of the relation of Area 6a to spasticity and most of our early extirpations of Area 4 encroached upon the posterior part of Area 6a. This accounts for the transient spasticity with "Area 4" lesions in chimpanzees reported by Fulton and Keller [10] in June, 1932, and by Jacobsen [13].

6a α alone or Area 6a β alone does not give rise to the full premotor syndrome, whereas complete removal, even if carried out seriatim, causes it.

Walshe states that the sequence of cortical ablation was so rapid in some experiments that the motor status in the affected limbs did not reach equilibrium before it was further modified by a second lesion. This was true in experiments in which the state of equilibrium was not the object of our study, but lest misconception arise from this criticism it should be pointed out that the survivals in our ablation studies are the longest on record. A number of our chimpanzees have been under observation for periods ranging from one to three years following a single operation; one animal was observed and trained for two years before surgical procedure was instituted, and was studied for a year after an Area 4 ablation (during which a state of paresis, markedly flaccid at first, persisted in the affected extremity). When the premotor area was removed the previously flaccid extremity became highly spastic, and has remained spastic for a period of two and a half years. The animal is still alive after a sojourn of five years in the laboratory; and it has been examined by every clinical neurologist who has honoured our laboratory with a visit. The specific reflexes of Rossolimo and Mendel-Bechterew, and the fanning sign of Babinski, also have persisted throughout this two-and-a-half year period. A full summary of our work on the frontal lobe which formed the basis of a series of Herter lectures will presently be published.

It would be unbecoming further to take issue with Walshe because his "motor area" includes our "motor and premotor areas"; and when he states that lesions of his "motor area" give rise to all the symptoms which we have relegated to the syndrome of the "premotor area" he is of course entirely correct, except that he omits "forced grasping," which, on wholly insufficient evidence, he vaguely attributes to disturbances in some other part of the frontal lobes. Such differences, therefore, as exist between us are primarily those of definition.

SUMMARY.

Since the anterior boundary of the excitable precentral cortex cannot be accurately defined in anatomical terms, and since the functions of the anterior part of the excitable cortex obviously differ from those of the posterior, a more precise terminology is needed to designate these functionally discrete regions. The term "premotor area" has been used in the past synonymously with the "intermediate precentral" region, but adequate anatomical definition has not hitherto been given. Since these regions correspond roughly with well-recognized cyto-architectural fields, it is suggested that the following conventions be adopted (fig. 1). That:—

(1) *Motor area* be restricted to the area giganto-pyramidalis, i.e. Area 4 of Brodmann, the Vogts and Foerster.

(2) *Premotor area*, which is also motor in function, include Area 6a (upper part) of the Vogts, the posterior part being designated 6a α and the anterior part 6a β.

(3) *Frontal association areas* include Areas 9, 10, 11 and 12 of Brodmann.

The term "excitable area" is applicable to both the motor and premotor regions.

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NOTICES OF RECENT PUBLICATIONS.

The Carotid Sinus and the Cerebral Circulation. By ERIK ASK-UPMARK. *Acta Psychiatrica et Neurologica.* Supplement VI. Copenhagen: Levin and Muskgaard. 1935. Pp. 374.

Ask-Upmark has studied the anatomical relationships of the carotid sinus in animals; he observed the effect of sinus stimulation on pial vessels, and analysed the blood-pressure records of 486 of Cushing's cases of cerebral tumour. The work indicates great industry and painstaking effort, but the size of the volume seems out of proportion to the new material it contains.

The most substantial contribution is the report of dissections of the sinus region in twenty-seven different species of animals. Evidence of a sinus (though unfortunately histological confirmation could not be carried out) was present in all. It lies on the occipital artery if the carotid is lacking, and is intimately associated with the glossopharyngeal nerve. In an effort to establish a relationship between the sinus and the vasomotor nerves of the brain, Ask-Upmark watched the pial vessels of the cat during stimulation. Vasoconstriction, though usual, was the passive response to a fall of systemic blood-pressure. Active dilatation, if present, was relatively unimportant.

The author's effort to prove arterial hypotension in patients with cerebral tumour and to link it with invasion of the hypothalamus and hypophysis forms the body of the section on clinical aspects of the problem. He found that the cerebral vascular changes are in the main secondary to systemic changes, but he fails to make a fair-minded review of the prior work of Weiss and Baker, who have made a detailed investigation of the heart and circulation in a considerable group of these patients. He dismisses too lightly their demonstration that some who lose consciousness and have convulsive movements on pressure of the sinus, do not have coincident decrease of pulse, of blood-pressure or of cerebral blood flow. In these persons there must be neurological mechanisms at work which are not dependent on circulatory changes, This contribution of Ask-Upmark's, serious and detailed though it is, can be considered as an introduction, not as a conclusion, to the subject of the carotid sinus in man.

Thérapeutique Médicale: Système nerveux. Par M. LOEPER, &c. Paris: Masson et Cie. 1935. Pp. 380. Price 50 fr.

This is the eighth volume of a system of therapeutics which has been edited by Professor Loeper. In its production he has obtained the collaboration of many well known neurologists and he consequently presents a review of French practice which must be interesting and instructive to English readers.

The first part, written by the Editor, deals with general principles, as the use of sedatives, hypnotics, analgesics and tonics. His presentation of these subjects is particularly valuable as he discusses the physiological and pharmacological actions of the drugs and other agents which he employs. The following chapters deal with the treatment of various diseases and pathological conditions as apoplexy, epilepsy, nervous syphilis, meningitis, migraine, &c., and with the use of fever therapy, radiotherapy in cerebral tumours, psychotherapy and the value of climate, baths and physical methods. Most of these chapters attain a high standard and are obviously written for the practitioner. Unfortunately the book lacks an index which would have added considerably to its value.

Les Névroses Tachycardiques. Par L. GALLAVARDIN et A. TOURNIAIRE. Paris: Masson et Cie. 1935. Pp. 121. Price 17 fr.

This small monograph deals with the nature and the symptoms of nervous tachycardia or irritable heart as observed in military and civil practice. The various disturbances of function associated with the rapidity of the pulse are fully described and analysed, and the conclusion is reached that all of them can be attributed to abnormal excitability of the cardiac sympathetic fibres. The many interesting observations recorded and the objective treatment of the subject make the book worthy of careful study.

Les Ramollissements Protubérantiels. Par J. O. TRELLES. Paris: G. Doin et Cie. 1935. Pp. 306. Price 50 fr.

A monograph on the common and variable groups of symptoms associated with softening of the pons Varoli is timely, for though so frequently met with in clinical practice and often studied from the anatomical point of view, there has been no recent attempt to deal comprehensively with the subject or to correlate accurately the disturbances of function with the sites of the lesions responsible for them. This the author has done by the study of a large number of personally observed cases and a survey of many collected from the literature.

As the position and the extent of the lesion depends on the distribution of the vessel which is occluded he naturally starts with the vascular supply of the pons; a fuller description of this would have been acceptable, that which he gives is very schematic. The symptoms are grouped into syndromes each of which is determined by the anatomical distribution of the artery which is blocked; this facilitates description, but it is obvious that even in this compact and highly organized portion of the nervous system many cases refuse to fall into any such rigid classification. This does not, however, invalidate the clinical and anatomical observations which are published. One of the most interesting symptoms occasionally associated with lesions of the brainstem, the so-called "palatal nystagmus," is discussed at length, and the author concludes that it is directly due to a special form of change in the bulbar olives—the so-called "olivary hypertrophy"—which is usually secondary to interruption of the central tegmental tract or of other fibres related to the olives.

Volume Jubilaire en l'honneur du Professor Dr. C. I. Parhon. Jassy: Brawo. 1934. Pp. 555.

In celebration of the 60th birthday of their eminent colleague, the Roumanian Society of Neurology, Psychiatry, Psychology and Endocrinology have published this volume of 55 papers on subjects in which Professor Parhon is interested. Only a small number are devoted to neurological subjects, but some of these, as that on compression of the cord by tumours, are valuable contributions. Others deal with psychiatric and criminological problems and with the functions and disturbances of the endocrine organs. The volume is a fitting compliment to a distinguished neurologist whose activities have been characterized by the generous scope of his interests.

Nouveau Traité de Psychologie. Par GEORGES DUMAS. Tome Quatrième. Les Fonctions et les Lois Générales. Paris: Librairie Félix Alcan. 1934. Pp. 528.

This rather tardy but welcome volume of the series is in two parts, of which the first deals with the general organizing functions of the mind and the second with the general laws of mental activity. In spite of the somewhat unprecise nature of these topics the treatment is neither diffuse nor obscure. Professor Piéron is the author of the first two chapters, dealing with attention and memory, together with habit; he presents the matter in a critical, undogmatic and matter-of-fact way. After Henri Delacroix's brief paper on the association of ideas, in which the Freudian contribution to this subject receives unduly meagre notice, there is a more abstruse chapter on Schematization by Revault d'Allonnes. Professor Georges Dumas then presents what is rather an essay on Symbolism than a scientific exposition; there is much discussion of symbols as used in ordinary language and literature, especially French, and in religion. Professor Dumas is very cautious in his views and scarcely mentions the more audacious theories as to the rôle of symbols in mental life. Professor Blondel writes a valuable but somewhat sceptical exposition of the notions of synthesis and automatism which have played so conspicuous a part in French psychology. Pierre Janet briefly reviews the normal and pathological facts which can be brought together under the conception of psychic tension and its oscillations. Professor Poyer's contribution deals with the difficult but very important subject of fatigue and intellectual work; it is incomplete in its survey of the relevant literature but covers most of the significant matters. The last chapter, on sleep and waking, is in the expert hands of Professor Claparède: it is a striking example of the spirit that appears in all the contributions to this work, in that it gives a balanced, critical account of what has been discovered, together with a full statement of the gaps and problems that remain.

Schizophrenia : Statistical Studies from the Boston Psychopathic Hospital, 1925-1934. Published by the Massachusetts Society for Mental Hygiene and the Boston Psychopathic Hospital. 1935.

Psychiatry is still in the stage at which statistical checks upon clinical belief and research are essential. In the eighteen papers here reprinted, a patient attempt has been made to study various aspects of schizophrenia and other conditions by the application of strict statistical methods to the data collected by psychiatrists and social workers. Professor Edwin B. Wilson, of Harvard, who directed the statistical work, points out in his foreword how trifling and even misleading in its apparent results may be the mechanical correlation of a huge number of items, and how desirable is the development and discussion of working hypotheses and the selection of a limited number of variables for study. Professor Macfie Campbell and his colleagues have been impressed during the research by the inadequacies in clinical records. These points are expanded in the various papers, which indicate that a strict investigation of this sort may at first appear to increase the difficulties of psychiatry by disposing of some easy generalizations and widely held assumptions, while clearing the way for further study and establishing some important correlations. There is in this collection very little that is new or surprising, but it is valuable for the critical outlook which informs the articles and the method of research pursued.

Life and Soul: Outlines of a Future Theoretical Physiology and of a Critical Philosophy. By MAX LOEWENTHAL. London: Allen and Unwin. 1934. Pp. 291. Price 8s. 6d.

The author of this work offers an interpretation of vital phenomena in which the conceptions are partly those of physics and partly of philosophy. His argument is clearly presented and well-knit but quite speculative, sometimes at variance with current physics and philosophy, and insufficiently related to the central problem here discussed though not clearly stated. His views on the spacial properties of psychic images seem untenable. The introductory chapter, in the first part of the book, deals with cellular structure and physiology, the next chapter with the general properties of living matter, and the third with chemical dynamics. There is a brief historical survey and then comes the second part in which philosophical considerations as to the outer and inner world are brought into the writer's general scheme.

Psychotherapie: Ein Lehrbuch für Studierende und Aerzte. Von H. KOGERER. Wien: Wilhelm Maudrich. 1934. Pp. 167. Price Rm. 10.

As in almost all manuals of psychotherapy there is here much more about psychopathology than about actual therapy. The reader seeks in a work with this title for advice as to the technique of treatment, the indications, the risks and the methods, but he finds only fifty-five pages dealing with these subjects, while there are thirty-three on the causes of mental disorder and seventy on the symptoms, mechanisms, and other clinical features of such illness. In this last clinical section there are also brief incidental references to psychotherapy, but the work as a whole is really a cursory textbook of psychiatry written from the standpoint of a psychotherapist who deals mainly with neuroses. The sections on treatment are sensible and are based on much experience. The customary half-historical, half-critical survey of the various European schools of interpretative morbid psychology is well done, though nowadays tedious through repetition. The many illustrative case histories are interesting as showing the author's material, methods and success.

Les Encephalities Psychosiques. Par L. MARCHAND et A. COURTOIS. Paris: Le François. 1935. Pp. 144. Price 25 fr.

The authors deal here with forms of cerebral infection which manifest themselves predominantly or only by mental symptoms. Their course may be acute, subacute or chronic, and while most are probably infective, in others intoxications or disturbances of metabolism may be the causal factors. Inflammatory changes can be generally demonstrated in the brain or its membranes in patients who succumb in the acute phases of the disease. The so-called Acute Delirious Mania is perhaps the commonest and best defined of the acute conditions, but other cases follow childbirth, surgical operations, and local or general infections as acute rheumatism or influenza. The large proportion of cases which occur among the insane is very striking. Emphasis is laid on the high figure of the blood urea which is almost constant.

The symptoms and the pathological changes in both the acute and chronic forms are excellently described in this small volume, which is undoubtedly a valuable contribution to a subject which has scarcely received the attention it deserves.

The Problem of Mental Disorder. A Study undertaken by the Committee on Psychiatric Investigations, National Research Council. Edited by M. Bentley and E. V. Cowdry. London: McGraw Hill Publishing Co. 1934. Pp. 388. Price 24s.

This account of the present outlook for research in mental disorder has greater scope and authority than any other work on the subject in English. The difficulty of the problem is frankly recognized; no attempt is made to extenuate our present ignorance and impotence with regard to a great deal of mental illness. The editors are not psychiatrists, but they have enlisted some of the foremost workers in this field in the United States, so that in the first part of the book Professor Macfie Campbell, Professor Adolf Meyer, Dr. Wechsler, Dr. Myerson and Dr. Kubie present different aspects of the clinical point of view. Dr. Kubie is a persuasive and modest representative of psychoanalysis. Apart from his contribution there is throughout the book evidence and even plain statement of a general impatience with the extreme claims of the psychoanalysts, unsupported as they are by any acceptable evidence. The second part of the book consists of papers on physiology, anatomy, biochemistry, biology and genetics, nutrition, endocrinology, psychology, pharmacology and anthropology, in which the bearing of such studies on the central theme is surveyed. Among the contributors here are Cobb, Cowdry, Penfield, Judson, Herrick, Minot, Yerkes, Bentley and other scientists of repute. In the face of the eager, not to say unprincipled, claims occasionally made for some individual method of study or treatment, it is salutary to have so honest, authoritative and hopeful a survey as that contained in this symposium.

Hallucinations et Délire. Les Formes Hallucinatoires de l'Automatisme Verbal. Par H. Ey. Paris: Félix Alcan. 1934. Pp. 192. Price 15 fr.

Dr. Ey brings together very clearly in this little book the views expressed in earlier papers which attracted attention among those interested in the problem of hallucinations. It is with psychomotor hallucinatory experiences that he is especially concerned. Discarding any atomistic view, he sees these as part of the whole delusional disorder, as an active expression of the patient's personality. It is upon the "error" rather than the sensory quality in the hallucination that he insists; he considers it the result of a fall in the psychic level determined by organic or by affective factors. After an introduction in which the notion of automatism in psychopathology is examined, there are chapters on the relation of hallucinations to images, language and inner speech, as well as on feelings of influence and passivity. The writer's views are put forward soberly and convincingly.

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-91, Great Titchfield Street, London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I to XXIII inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.

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SEPTEMBER, 1935.

BRAIN.

PART 3, VOL. 58.

THE ORIGIN OF THE BERGER RHYTHM.

BY E. D. ADRIAN AND K. YAMAGIWA.

IN a recent paper Adrian and Matthews (1934*b*) have discussed the origin of the Berger rhythm, the characteristic oscillation of electric potential on the surface of the head reported by Hans Berger in 1929. It consists of a series of waves with a frequency of about 10 a second, and an amplitude of 0·05-0·1 millivolts, appearing when the subject is at rest with eyes closed and disappearing when the eyes are opened or when the attention is fully engaged. Berger (1929-35) has shown that the potential waves originate in the brain and has made a detailed study of the factors which influence them. Adrian and Matthews repeated and confirmed many of Berger's observations but gave a different interpretation of the rhythm. This was based on the view that the activity responsible for the potential waves is confined to the occipital lobes, whereas on Berger's interpretation the whole cortex is involved. The present work was undertaken to supply more definite evidence on this question, since it is of critical importance in deciding the nature of the rhythm.

Berger supposes that every part of the cortex, when active, gives rise to potential waves at 10 a second. The disappearance of the rhythm when the eyes are opened is due to a widespread inhibition, the excitation of a part of the brain causing an inhibition elsewhere with the result that the potential changes (though actually larger in the excited region) are no longer perceptible through the skull. This view depends on the fact that the potential waves can be detected in almost any part of the scalp. It was criticized by Tönnies (1933) on the ground that the potential changes, though perceptible elsewhere, appear to arise only from the occipital part of the brain. Adrian and Matthews, for the same reason, suggested that the rhythm is a spontaneous or resting discharge from a large group of neurones in the occipital lobe, neurones mainly concerned with vision. When the eyes are shut these are left undisturbed and are free to beat in unison at their natural period; when the eyes are opened the different units must work at different rates and a synchronous beat is no longer possible.

Adrian and Matthews argued for an occipital origin because the potential changes are much greater over the occipital part of the head than over the frontal. They argued that the active region must be concerned with vision (*a*) because the rhythm is abolished far more effectively by visual stimuli than by any other kind, and (*b*) because exposing the eyes to a flickering field gives rise to potential waves with the same general distribution over the head but with the frequency of the flicker instead of the usual 10 a second frequency of the Berger rhythm. They found, however, as Berger had done, that the waves recorded simultaneously from two different parts of the skull were not always in phase and might change their phase relation from time to time. To account for this they had to suppose that the focus of the activity was not at a fixed point, but might shift over a fairly wide area at the back of the head. The extent of the area was not decided, but it was recognized that the next step must be to map it as accurately as possible, and that no explanation of the rhythm could be considered satisfactory until this had been done.

The present work is concerned primarily with this question of the localization of the focus of activity and the extent of its movement. Our method has been to map out the distribution of potential over the head from moment to moment by recording simultaneously from different points with three and sometimes four oscillographs. Our conclusion is that the Berger rhythm is commonly due to an activity which has a focus in the occipital region of each hemisphere. In some individuals the focus seems occasionally to overstep the limits of the occipital lobe, but as a rule it is confined to this lobe, shifting its position from time to time. Although the beat may arise within a relatively large area we do not think that the explanation put forward by Adrian and Matthews needs to be modified except in some unimportant details.

METHOD.

The apparatus used for mapping the potential gradients consists of four separate amplifiers and oscillograph systems arranged to record simultaneously on bromide paper. It is almost identical (apart from the introduction of a fourth oscillograph) with the three oscillograph systems used by Adrian and Matthews (1934*a*) for mapping potential distributions on the exposed cortex of animals. The essential feature in each of the amplifier sets is the balanced (push-pull) input stage introduced by Matthews (1934), for this avoids the necessity of earthing one of each pair of electrodes. As a rule a small coupling condenser (0·1 mf.) was used in each amplifier to prevent slow movements of the base line, but, as this would lead to some distortion of the waves, controls were made from time to time with large condensers (2 mf.) in place of the small. Three of the oscillographs were of the Matthews optical type (period about $\frac{1}{6000}$ second). The fourth was a Matthews ink-writer oscillograph (period $\frac{1}{40}$ second) with a light pointer attached to the writing arm and arranged to throw a shadow at the side of the film. Sensitivity was adjusted by a tapped volume control in each set. The performance of the system can be judged from fig. 1, where all four oscillographs are connected to the same pair of electrodes and should give identical records. The ink-writer oscillograph cannot follow the most rapid excursions and sometimes lags behind the others when there is a sudden large movement. In spite of this it has been of great value to have records from four sets of electrodes instead of three only.

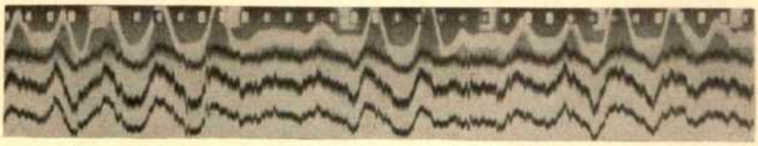

FIG. 1.—Four oscillographs connected with the same pair of electrodes. The records should be identical, but the top tracing is made by an ink-writer oscillograph of low period and does not show the small, rapid deflections present in the others. Subject sitting with eyes closed. The maximum potential change is about 70 microvolts. Time marker (above) four spaces equal one second.

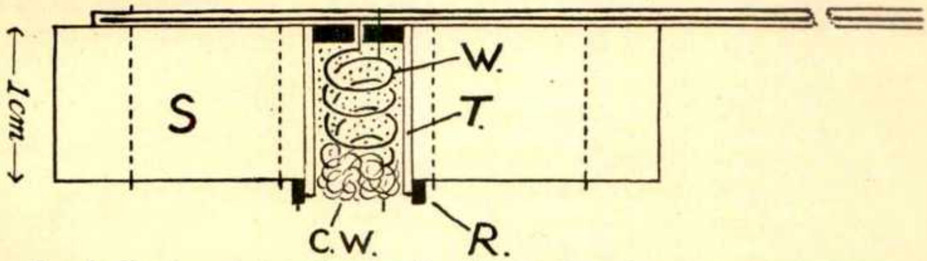

FIG. 2.—Diagram of electrode. S, rubber slab; T, glass tube; W, spiral of silver wire coated with silver chloride; C.W. cotton-wool in gelatin; R, rubber guard ring.

The electrodes were moist pads held in contact with the scalp by a rubber bandage. After trying various forms we found that the most convenient was that shown in fig. 2. A short length of glass tube

7 mm. in diameter is plugged with cotton wool and filled with gelatin jelly made up with saline. At the closed end of the tube is a coil of silver wire coated with silver chloride. The cotton wool protrudes from the open ends and is moistened before use with saline, but the moisture is prevented from spreading over the scalp by a rubber ring surrounding the end of the tube. The electrode is held in a rectangular slab of rubber which can be bandaged to the surface of the head. A photograph showing six of these electrodes in position is given in fig. 3.

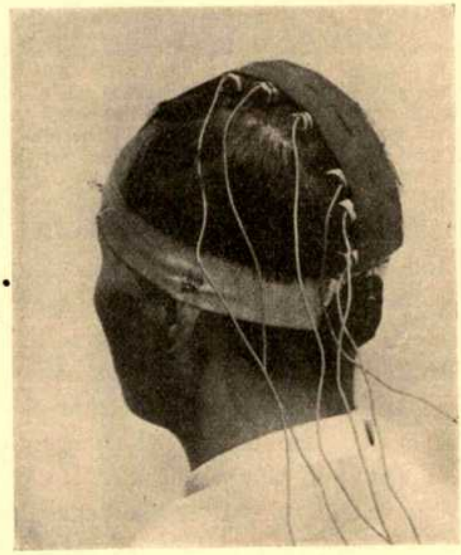

FIG. 3.—Electrodes in position along median line in K.Y.

In the earlier experiments the subject, either K.Y. or E.D.A., sat with the head resting on a pillow to allow the neck muscles to be relaxed. The experimenter gave the order to open or close the eyes and recorded the onset and failure of the rhythm as well as its course whilst the eyes were closed. Many long records were taken on slowly moving paper to detect occasional abnormalities in the potential distribution. To map out the gradients in the back to front direction the electrodes were arranged in the mid-line and the distance of each from the nasion was measured in inches.[1] Dr. Barclay kindly made X-ray photographs of our skulls in the median plane and from these contour diagrams were made on which the correct position of the electrodes could be marked. These diagrams are attached to most of the records which follow. Six other subjects were investigated by the same method after the details of the technique had been worked out on ourselves.

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[1] For our failure to measure in centimetres we can only offer the inadequate excuse that our tape measure gave only inches.

RESULTS. DISTRIBUTION OF POTENTIAL IN THE MEDIAN PLANE.

When the electrodes are arranged along the mid-line the records of the Berger rhythm always show long stretches in which the maximum electrical activity is clearly in the occipital region. Two such records are given in figs. 4 and 5. The electrodes are spaced at intervals of 2 to 3 in. and in both records the waves recorded from the hindermost pair of electrodes (bottom tracing) are in the opposite sense to the waves at the other two pairs. This is represented by the V-shaped marks on the skull diagram. The direction of the waves shows that the potential gradients on the scalp come to a focus near the electrode at 13 in. from the nasion. The reversal of the gradients of this point is not enough, in itself, to show that the maximum change occurs there: for if it were in the frontal region, the gradients would converge towards the occiput because the potential there would not change at all. But the maximum is certainly in the occipital and not the frontal region,

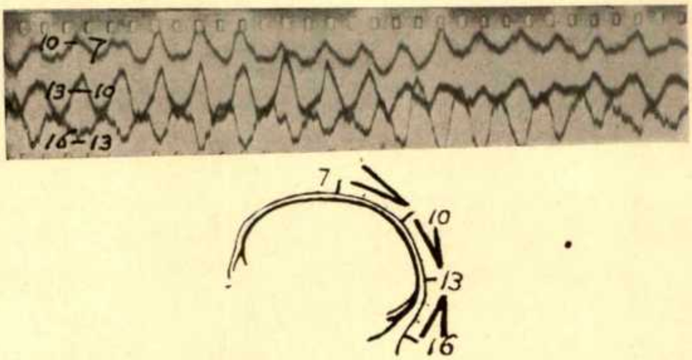

FIG. 4.—Potential waves of Berger rhythm in E.D.A. recorded with three oscillographs from electrodes in positions shown in skull diagram. Focus at 13 in. from nasion.

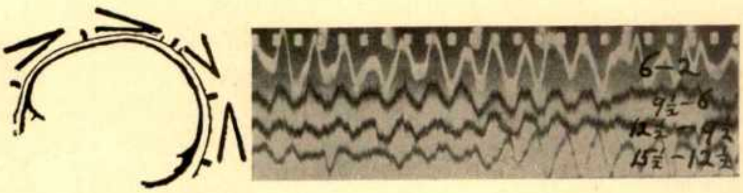

FIG. 5.—Potential waves of Berger rhythm in K.Y. recorded with four oscillographs.

for the waves recorded with one occipital electrode and one on an indifferent part of the body are very much larger than those with a frontal electrode instead of the occipital. Further proof is given by the fact that the potential gradients become much steeper towards the back of the head. In fig. 5 this is not evident, for the oscillographs were not adjusted for equal sensitivity, but the relative sizes can be seen in their correct proportions in fig. 6 where all the oscillographs are equally sensitive and the electrodes are spaced at equal intervals.

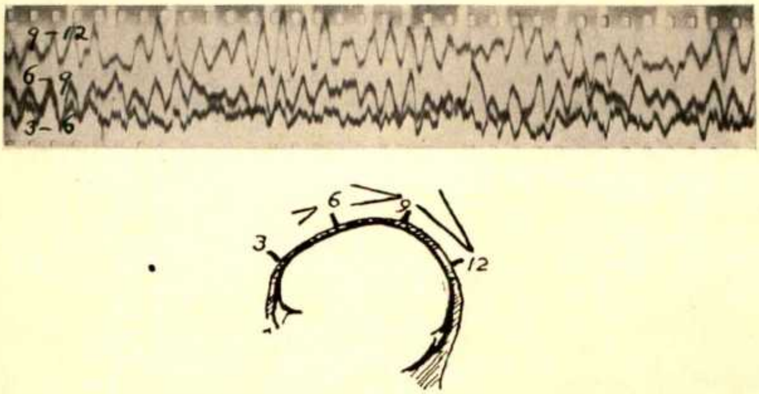

FIG. 6.—Waves in K.Y. shown in correct proportion, with oscillographs at equal sensitivity and electrodes at equal intervals.

In figs. 4 and 5 the waves from each pair of electrodes preserve the same phase relation throughout the record but not the same relative size. Presumably the focus, i.e. the point at which the potential gradient is reversed, shifts slightly, though never enough to reverse the average gradient between any two electrodes. But in any long record, from E.D.A. or K.Y., there are periods when the focus shifts considerably. A shift in the caudal direction is illustrated in figs. 7 and 8 which are from the same experiments as figs. 4 and 5. In both of these the gradients during the first part of the record come to a focus at a point some distance above the external occipital protuberance, but in the latter part the focus seems to have moved round towards the base of the skull, for the waves from the lowest pair of electrodes are now in phase with the others.

Clearly the first point to decide is how far the focus can shift in either direction. We cannot follow it round the base of the skull, for as soon as the lowest electrode comes to lie on the neck muscles it leads in effect from the whole undersurface of the skull; but the limit upwards and forwards can be determined by taking long records with various spacing of the electrode. Our first attempts to do this gave uncertain results, for we used electrodes spaced too far apart. It will be seen from the diagram in fig. 9 that with wide spacing the gradient may seem to reverse at a considerable distance from the true focus. However, it is quite possible to work with the electrodes close together and to explore the whole circumference of the head systematically with four or five electrodes in line one inch apart. By this method it was

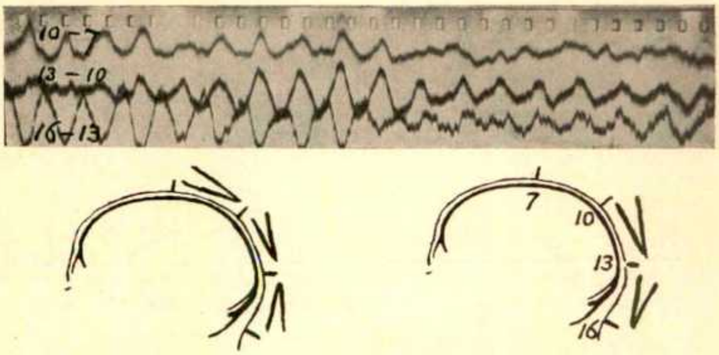

FIG. 7.—Movement of focus downward. Record from E.D.A.

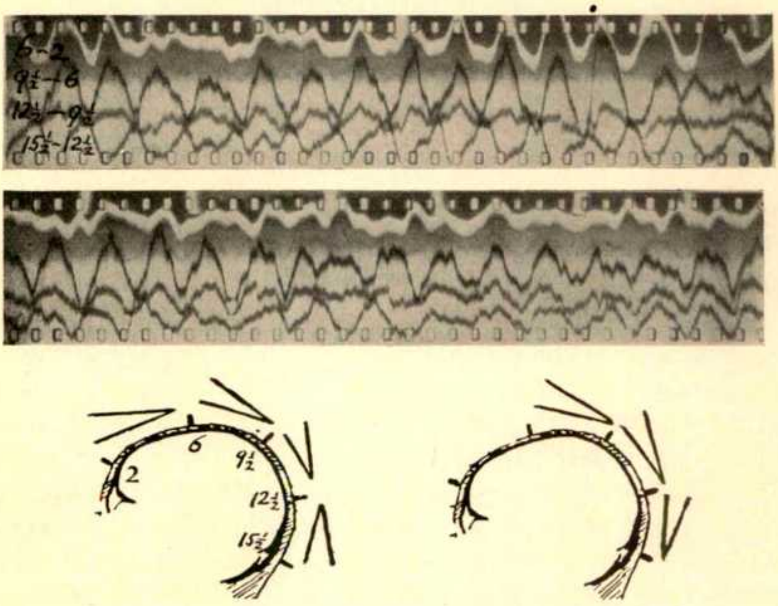

FIG. 8.—Movement of focus downward. Record from K.Y.

found that over the whole line from about 5 to 12 in. from the nasion in K.Y. and 5 to 10½ in. in E.D.A. the waves, if appreciable at all, were in the same direction. Behind the 12 in. point and sometimes in front of the 5 in. point the waves might be reversed, though in the frontal region they are so small that the electrodes must be spaced further apart to give a clear record of them.

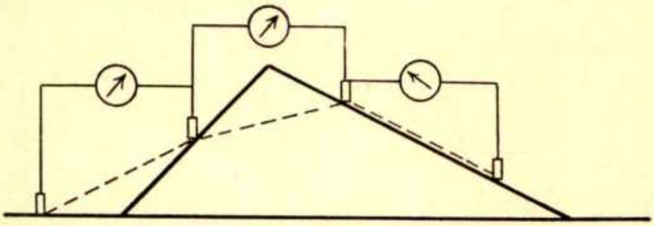

FIG. 9.—Error in estimation of focus due to wide spacing of electrodes. Black line gives true potential gradient, dotted line observed gradient. Hypothetical case.

We shall deal first with the reversal area at the back of the skull where the gradients are steep. Though the forward limit is 12 in. in K.Y. and 10½ in. in E.D.A. it was only on rare occasions that the reversal point was further forward than 13 in. in K.Y. and 11½ in. in E.D.A. Fig. 10 gives a sample of the type of record on which this conclusion is based. In record A the waves in the region between 10 and 13 in. are always in phase and remained so throughout a record lasting for several minutes. In record B they are in phase at 11-12 and 12-13 in., and opposite in phase at 13-14, and in C the waves at 13-14 and 14-15 in.

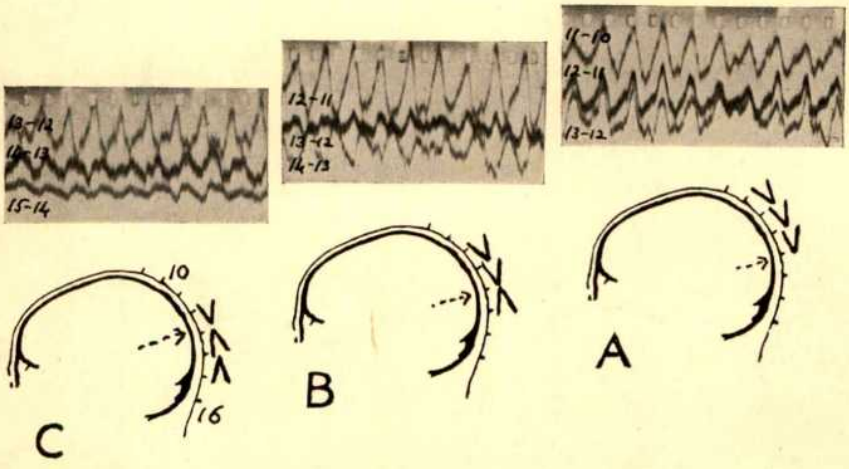

FIG. 10.—Records from K.Y., with electrodes closely spaced. Focus at 13 in. from the nasion.

go together and are opposite in phase to those at 12-13. The focus is therefore at 13 in.; though in both the latter records there were periods (not shown in the figure) when the waves were in phase in all three oscillographs, the focus having shifted downwards as in figs. 7 and 8.

The extent, in E.D.A. and K.Y., of the occipital region in which the reversal may occur is shown on the skull tracings in fig. 11. The differences between us seem to be mainly due to the difference in the shape and size of our skulls, for the distance from nasion to inion is 1½ in. less in E.D.A. than in K.Y.

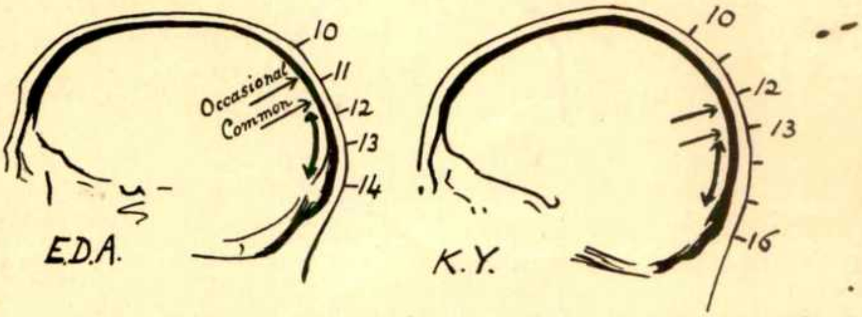

FIG. 11.—Tracings of X-ray photographs of skull from E.D.A. and K.Y., showing the region within which the maximum potential change is found.

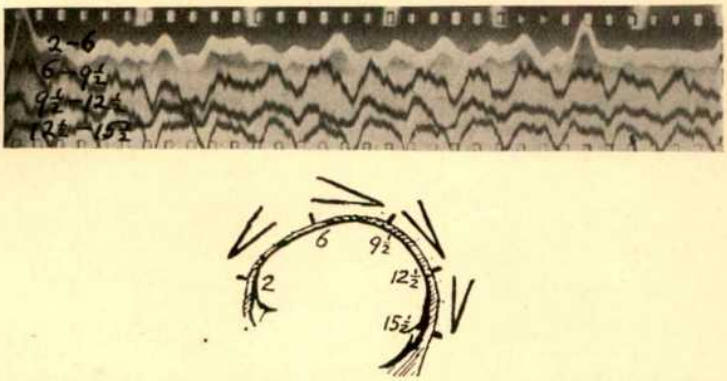

FIG. 12.—Record from K.Y., showing reversal of waves in the frontal region. The oscillograph from the frontal electrodes (white line) is working at greater sensitivity than the rest as the changes are very small.

The frontal area in which reversal sometimes occurs is not indicated in the figures. It is difficult to estimate its size, as the waves here are very small and may be obscured by action potentials from the facial muscles. A record showing the reversal in the frontal region is given in fig. 12 and it occurs in one place in fig. 6 (in both of these the electrodes were widely spaced). From experiments with closer spacing it does not appear that the reversal point was ever more than 5 in. from the nasion. In the six other subjects examined the same general distribution of potential was found. In all of them the gradients were in the same direction over a length of 5-6 in. on the top of the head, the reversal occurring in the occipital region. In two of them, however, the focus was much more stable than in K.Y. or E.D.A., never moving far down towards the base of the skull and remaining within the narrow limits shown for one of them in fig. 13. The range of movement was not found to vary appreciably from one day to another, either in these cases or in those with the wider range.

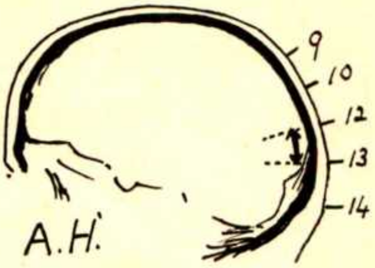

FIG. 13.—Tracing of X-ray photograph of A.H.'s skull, showing region of maximum potential change. Compare with fig. 11.

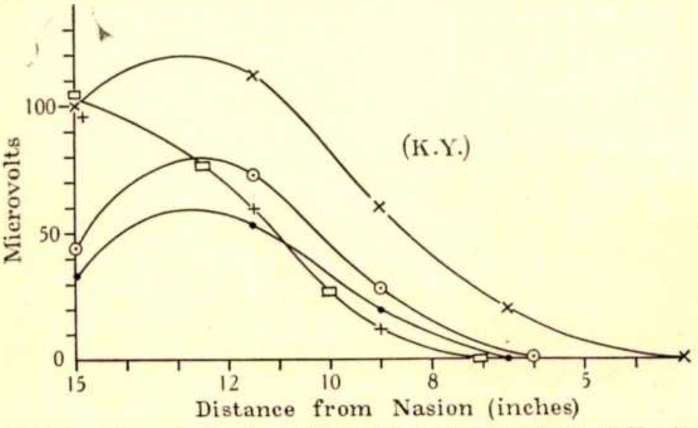

FIG. 14.—Potential gradients along the mid-line of the scalp in K.Y., from various records. The shape of the curve near the maximum is conjectural. The potentials given are measured from the trough to the crest of the wave.

The results in the case of K.Y. are summarized in the curves in fig. 14 which give the potential gradients for a number of waves selected at random. Since it is impossible, when the electrodes are closely spaced, to make simultaneous records covering the whole length of the head, the curves do not always include the point where the gradients are reversed. They show, however, that the gradients have the same general form in relation to the reversal point wherever this may be. Curves from the subject A.H. are given later in fig. 21B.

DISTRIBUTION OF POTENTIAL ON THE LATERAL ASPECT OF THE SKULL.

The potential gradients along the horizontal circumference of the head have been investigated in the same way by recording with three or four oscillographs. The electrodes were placed on a line drawn along either side of the head, from nasion to inion, or on a line parallel to this but an inch higher.

In every subject examined it was found that if two pairs of electrodes were placed one on either side of the head at distances anywhere between 3 and 8 in. from the inion, the waves always had the same phase relation, the potential gradients converging towards the back (or front) of the head. The relative size of corresponding waves on either side was not constant, and occasionally the rhythm was present for a few beats on one side and absent or too small to detect on the other, but evidently the two sides are so closely linked that the phase relation cannot vary.

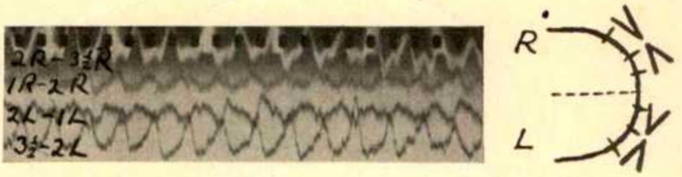

FIG. 15.—Record from A.H., with electrodes arranged laterally. Focus on either side 2 in. out from mid-line.

When one side is explored in detail it is found, as with the records from the mid-line, that over most of the lateral aspect of the head the waves are always in phase. In the occipital region there is a reversal of the gradient, usually at about 1 to 2 in. from the mid-line. A comparison of records made from either side of the head shows that as a rule there is a distinct focus of activity in either hemisphere. In fig. 15 the two foci are shown in a single record, but such records are uncommon, for with four oscillographs they can only be obtained when the potential changes on either side of the mid-line are approximately equal and when two of the electrodes happen to lie very near to the focal points. The two foci are sometimes so close to the mid-line that they coalesce, and sometimes the potential is greater on one side and so masks the presence of a focus on the other. The diagrams in fig. 16 illustrate how these difficulties arise when the electrodes are widely spaced in the attempt to cover the whole region in a single record. But records from one side with closer spacing of the electrodes rarely fail to show a focus

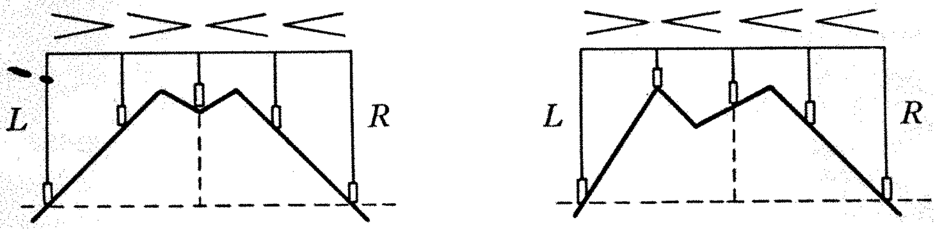

FIG. 16.—Failure to detect double focus owing to spacing of electrodes, asymmetrical gradients, &c.

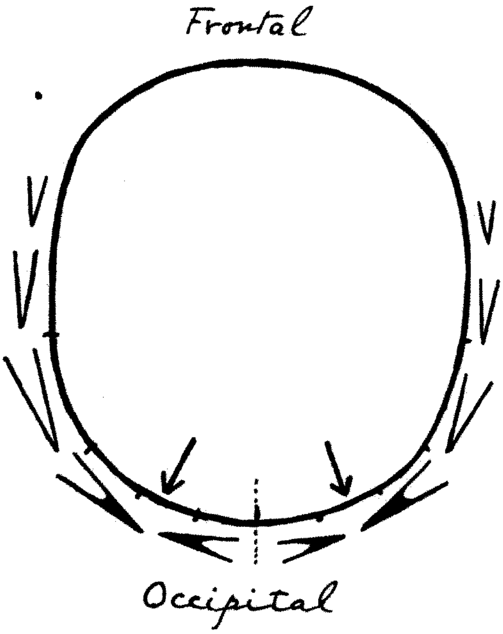

FIG. 17.—Magnitude and direction of waves recorded laterally. The diagram is based on records from K.Y. and A.H. It is not to scale and the focus is represented as stationary. Actually it may be in any position from the mid-line to 2½ in. out.

of activity somewhere near the mid-line and presumably, if there were enough oscillographs to make them, simultaneous records from the other side would show a focus there as well.

From time to time the focus shifts laterally as it does vertically, the limit of outward movement being about 2 to 2½ in. from the mid-line.

The shift is not necessarily symmetrical on either side, and as the potentials are often greater on one side than the other it is probable that the active areas may be unequal. We have not observed any reversal of the gradients in the frontal region, but as a rule it is impossible to detect any waves in the region between the centre of the forehead and 4 in. to either side. As with records from the median plane the gradients become progressively steeper towards the back of the head.

These findings are summarized in the diagrams in fig. 17 for the two subjects K.Y. and A.H.

ORIGIN OF THE POTENTIAL CHANGES.

(*a*) *Possible muscular origin.*—Fig. 18 shows the regions of maximum potential change at the back of the head in the subject A.H. It immediately suggests two possible sources for the Berger rhythm. The active regions might be (*a*) the occipital lobes of the brain or (*b*) the occipital part of the epicranius (occipito-frontalis) muscle. It is true that the evidence for a cortical origin of the Berger rhythm is fairly conclusive. Moreover, a peculiar type of muscular activity would be needed to produce the characteristic wave form of the Berger rhythm and there is no reason to suppose that the epicranius muscle would develop such activity when the eyes are closed. There is, however, a simple way of deciding whether this muscle is concerned. The epicranius is supplied by the 7th nerve and so in a case of facial paralysis (Bell's palsy) the muscle will be paralysed on one side of the scalp but not on the other. Will this make any difference to the magnitude or direction of the potential waves recorded from either side of the head?

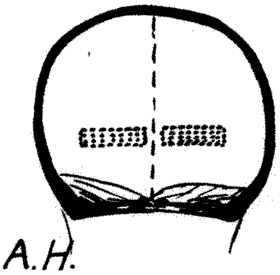

FIG. 18.—Tracing of skull of A.H. viewed from behind, showing areas in which the foci are to be found.

Only one case has been examined, but the results were quite definite. The paralysis had lasted six weeks and there was already a slight degree of recovery in the facial muscles, but the movement of the scalp showed that there was no contraction in the occipitalis on the affected side when the patient was asked to raise his eyebrows, although on the sound side the contraction was well marked. In spite of the unilateral paralysis of the scalp muscle simultaneous records of the Berger rhythm from either side of the head gave the normal distribution of potential. The waves from the right side of the head were no smaller than those from the left. Even more conclusive is the fact that, as in normal subjects, there was a reversal of the potential gradient an inch or more from the mid-line on either side. The existence of a distinct focus to the right of the mid-line can be seen in fig. 19. Since this focus is immediately over the paralysed muscle we can safely rule out the epicranius as a source of the Berger rhythm.

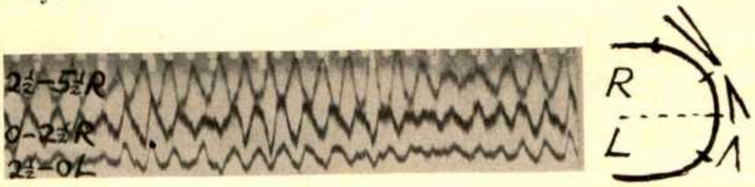

FIG. 19.—Record from E.T., with paralysis of right occipitalis muscle. Potential gradients as usual. During the record the change is greater on the right side than on the left.

(*b*) *Cortical origin.*—There is no reason to doubt the possibility of detecting cortical potential changes through the unopened skull, for Kornmüller (1933) and Tönnies (1933) have shown that this can be done in animals. For the potential changes of the Berger rhythm the evidence for a cortical origin has been given in detail by Berger and confirmed by Adrian and Matthews. But the latter authors have pointed out that the potential distribution over the scalp may be modified considerably by the existence of a large defect in the bone. It is conceivable, therefore, that the distribution of potentials which we have found in the normal subject might depend on the physical properties of the medium enclosing the brain, i.e. the resistance of the skull in different parts, the presence of blood sinuses, etc.

As against this there is the fact (*a*) that the distribution of potential is by no means constant, the focus shifting an inch or more in a single record; and (*b*) that the resistance of the skull is not markedly less in the occipital region than elsewhere. It is true that our evidence for the last statement is scarcely conclusive, for we have examined only two skulls and by a method of no great accuracy. Small cylinders of bone were removed from the skulls within forty-eight hours of death. A cylinder of bone was set up in line with a cylinder of the same dimensions cut from a block of fixed animal tissue or of gelatin made up with saline, and three non-polarizable electrodes were arranged, two at the exposed ends of the cylinders and one leading from between their opposed faces. A potential of 0·05 millivolts was applied suddenly between the ends of the cylinders and the resulting potentials between the different electrodes were recorded by an amplifier and oscillograph. As the amplifier was condenser coupled only the initial value of the deflection was measured. By comparing the fall of potential over the two cylinders, it was found that the resistance of the bone was eight to fifteen times as great as that of the corresponding cylinder of tissue in saline; but the resistance of the skull did not vary with its thickness and was evidently due to the denser outer and inner tables. In one case a cylinder from the occipital bone 5 mm. thick had a resistance 1¼ times as great as a cylinder 8 mm. thick from the frontal bone of the same skull.

The skull will therefore interpose a high resistance layer between the cortex and the scalp, and this will deprive the potential map of much of the detail and sharpness of outline which it would have if the electrodes were applied directly to the cortex. Yet, assuming that the skull resistance is uniform, a reversal of the potential gradients at a point on the scalp will imply a reversal in the cortex immediately beneath. There are, no doubt, irregularities in the skull resistance which might distort the scalp map to some extent, but hardly to the extent of shifting the whole region in which the reversals are found to occur.[1]

We have attempted to check these arguments by establishing potential gradients within the skull and finding the corresponding distribution over the scalp. The observations were made on a cavader four days after death. To produce a potential change corresponding with what might be expected to occur in the cortex we used a disc of thin rubber 1¼ in. (3 cm.) in diameter covered on either side with copper wire gauze to which insulated wires were attached. The metal faces of the disc were connected with a coil placed over a rotating magnet and giving a potential oscillation of a few millivolts at a frequency of 10 a second. The disc was placed on the surface of the cortex in various regions and the dura, skull and scalp were closed over it, cracks in the bone being stopped with plasticine. Electrodes leading to the three oscillographs were bandaged onto the head in the usual way and records were made of the potential waves in the scalp.

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[1] See the valuable analysis of the current distribution through the skull given by Tönnies (1933).

The object of the experiment was to find out how closely the position of the disc could be located by records from the scalp. Those given in fig. 20 show that the localization is reasonably close. The scalp waves are reversed: (*a*) In the occipital; and (*b*) in the precentral region according to the position of the underlying disc; and in (*c*) the focus is slightly to the right of the mid-line when the disc is slightly to the right.

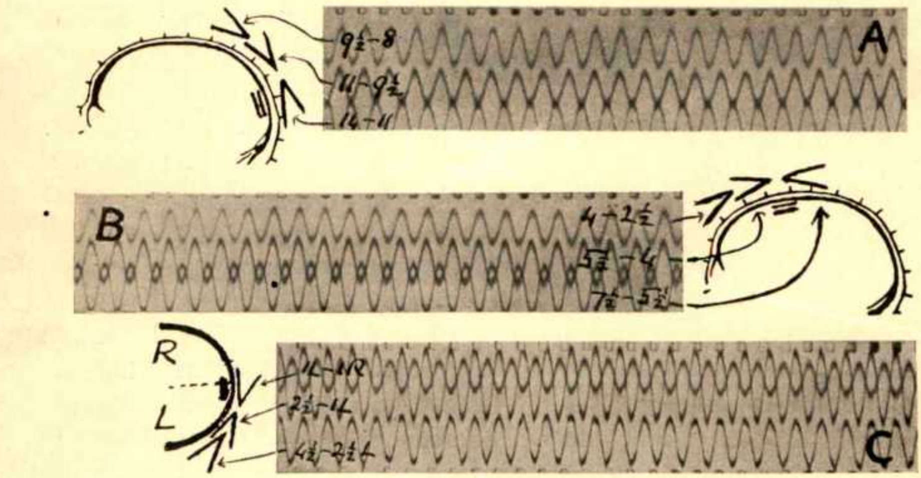

FIG. 20.—Records from cadaver. Potential waves at ten a second, due to rotating generator connected to disc on cortex. Scalp electrodes and disc in positions shown in diagrams.

A. Centre of disc 11¾ in. from nasion. Gradient reversed at 11 in.
B. Centre of disc 6 in. from nasion. Gradient reversed at 5½ in.
C. Centre of disc ½ in. to left of mid-line. Gradients reversed at 1 in. from mid-line.

By exploring with electrodes close together it was found that a shift of 1 in. in the position of the disc could be readily detected. It was also found that there was no sign of distortion of the potential distribution on the scalp, either in the lateral or in the back to front direction.

It is interesting to compare the potential gradients set up artificially with those occurring naturally. Fig. 21 A shows the potential gradients in the cadaver produced by an oscillation of 1·8 millivolts applied to the disc on the surface of the occipital lobe. The abscissæ give the distance of the scalp electrodes from the nasion and the position of the disc. Fig. 21 B gives the gradients for three waves of the Berger rhythm in the subject A.H. This subject was chosen for the comparison because in him the steadiness of the focus enabled the electrodes to be placed in the best positions for mapping the gradient. The likeness between the two figures is remarkable; indeed the only clear difference is that the potentials are three times as large in fig. 21 A as in fig. 21 B.

With the artificial system the potential change on the scalp between the front and back of the head is about one-tenth of that measured between the two sides of the disc (*in situ*). A ratio from 4 to 8 per cent. between the recorded and the applied potentials was found in another cadaver, using sudden potential changes instead of repeated waves. With a disc ¾ in. (2 cm.) in diameter the ratio fell to about 1 per cent. Thus an active region 1¼ in. in diameter should give waves of the size found in the Berger rhythm (about 0·05 mv.) for a potential of 1 mv. or less between active and inactive regions on the surface of the cortex. This is well within the range of the potentials which can be recorded

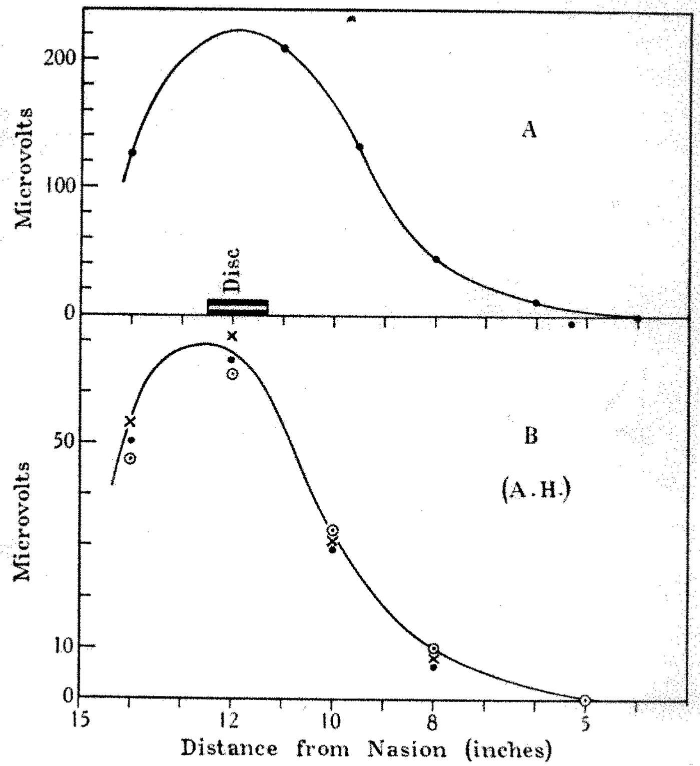

FIG. 21.—Comparison of gradients produced artificially (A), and gradients during Berger rhythm from A.H. (B). Readings are given for three successive waves of the Berger rhythm.

from the exposed cortex in animals. It is true that the current distribution round an active region in the cortex must be different in many respects from that round a metal-coated disc lying on the surface; it is satisfactory, however, to find that the artificial system does not need impossibly large potentials or an impossibly large active area to give potential waves of the right order on the scalp.

Since there is no evidence of distortion due to the skull it must be concluded that the main focus of activity for the Berger rhythm is in the occipital part of the cortex. If there are other active regions as well, the potential changes due to them are not great enough to influence the gradients on the scalp in a recognizable way. There is the occasional reversal in the frontal region, but this would be a natural consequence of a focus of activity in the lower part of the occipital region. The current flow in the scalp will converge towards the point of maximum potential change and must diverge from a neutral point opposite, as in fig. 22 A. With some of our subjects it appears that the occipital focus is usually too high up and the neutral point too far down for the frontal reversal to appear, but it may do so when the occipital focus moves down to the position shown in fig. 22 B. This explanation agrees with the fact that the frontal reversal is only found when the region of maximum change shifts round towards the base of the skull; also with the fact that a frontal reversal was produced in the cadaver by moving the disc into the position shown in fig. 22 B.

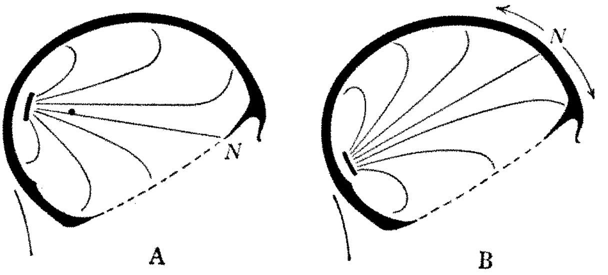

FIG. 22.—Reversal of waves in frontal region due to neutral point there. In A the neutral point (N) is too far down, but in *B* the focus of activity has moved down and the neutral point up. The frontal reversal would therefore appear.

CORTICAL AREA RESPONSIBLE FOR THE RHYTHM.

The extent of the area in which the maximum potential change can occur has been shown already in figs. 11 and 13. In A.H. (fig. 13) it would correspond to an area on the cortex lying well within the margins of the occipital lobe, but in E.D.A. and K.Y. the area must extend above the parieto-occipital sulcus. This may be seen from fig. 23 in which a map of the cortex is fitted to the X-ray tracing of E.D.A.'s skull. Although Area 19 rises higher laterally than in the midline it does not seem large enough to account for all the positions to which the focus may move. We must also reckon with the fact that the focus marks the centre and not the boundaries of the active region. The observations in the previous section show that the active region behaves as though it were concentrated into a disc 1 or 2 in. in diameter ~~but~~ it is quite possible that similar potential gradients would result if some of the active units were scattered over a larger area.

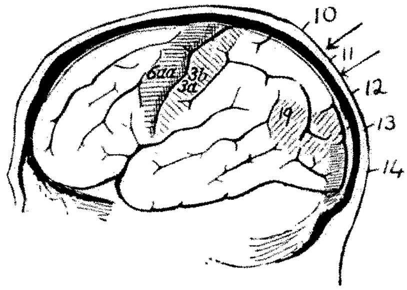

FIG. 23.—Map of cortex fitted to tracing of E.D.A.'s skull.

It is probable, then, that the activity which gives rise to the Berger waves may extend beyond the margins of the occipital lobe; indeed the focus itself may move outside the occipital area for a few beats. On the other hand, for most of the time the maximum activity is strictly occipital; in some individuals it must lie within the margins of the lobe for 99 per cent. of the waves, in others for 95 per cent. On rare occasions we have found a single wave or a series of two or three in a long record arising, apparently, from a focus well outside the limits shown in fig. 11, though this occurs so seldom that we have not been satisfied that the result was not due to distortion from muscle action potentials, &c. But there is no doubt that the focus can shift over a considerable region which varies from one subject to another and does not seem to correspond precisely with a particular anatomical field. It is therefore unlikely that there is any hard and fast limit to its movement and all that can be said is that the great majority of the waves are produced in the occipital lobes. It is unlikely that many of the waves come from the striate area, for the focus is often as much as 2 in. from the mid-line on either side. The magnitude of the potentials makes it unlikely that they are derived from regions below the cortex, for there the amount of short circuiting would be much greater.

MOVEMENTS OF THE FOCUS.

The way in which the focus may shift from place to place is consistent with the idea of a spontaneous beat arising within a large group of neurones. The shift often takes place suddenly, the potential distribution changing in the course of a single beat and showing no sign of a gradual movement from the old position to the new. This can be seen in the records in figs. 8 and 9, where there is a sudden shift towards the base of the skull. But most records of the Berger rhythm will show regions of periodic increase and decrease in the size of the waves, and during these there is often a gradual movement of the focus. An example is given in fig. 24 where the focus moves down gradually from a position above 12¼ in. to somewhere between 13¼ and 14¼ in. If only one oscillograph were in use and the electrodes were at 12¼ and 15¼ in. the maximum potential would be very large in the middle of the record where the waves from all three oscillographs are in phase and very small at the end where I and III are opposite in phase. Thus an apparent waxing and waning in activity, if recorded from one pair of electrodes, may be due mainly to a shift in the focus. Needless to say the changes in size of the waves are often due to genuine fluctuations in the activity of the cortex, depending probably on fluctuations in the number of neurones which take part in the beat.

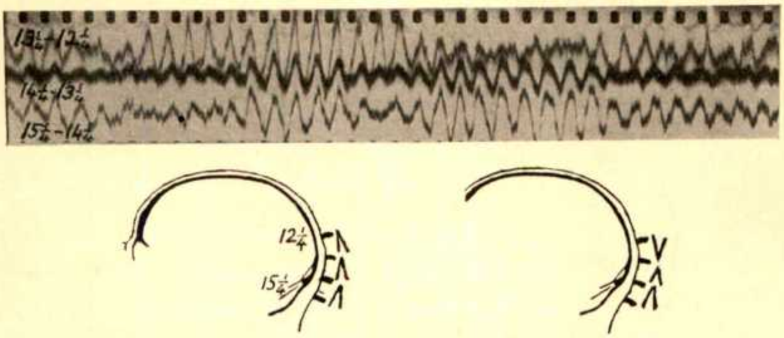

FIG. 24.—Record from E.D.A., showing gradual movement of the focus.

It is interesting to find that fluctuations in activity are often accompanied by a characteristic change in the nature of the beat. When this proceeds regularly with little variation in size, the maximum oscillation of potential occurs at a fixed point. The change in the nature of the beat is shown in fig. 25. The waves fall out of step with one another so that the crests and troughs no longer occur at the same moment in all three oscillographs. An analysis of the potential gradients in a series of such waves is given in fig. 26. There is no longer a stationary focus; instead each wave seems to pass along the line of electrodes, the focus of the activity occurring first at electrode 2, then at 3 and finally at 4, though by the time it reaches 4 the wave has almost subsided.

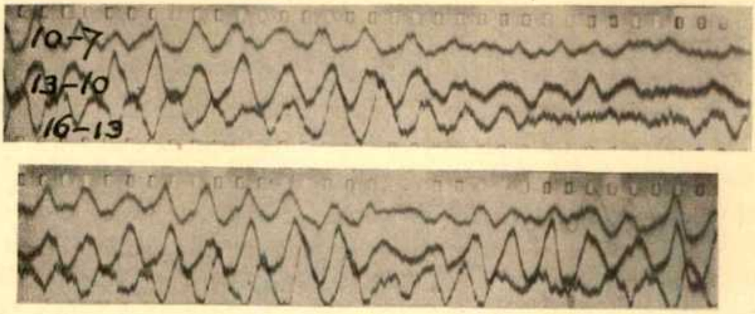

FIG. 25.—Records from E.D.A., showing "moving waves," the crests and troughs no longer coinciding in all three oscillographs.

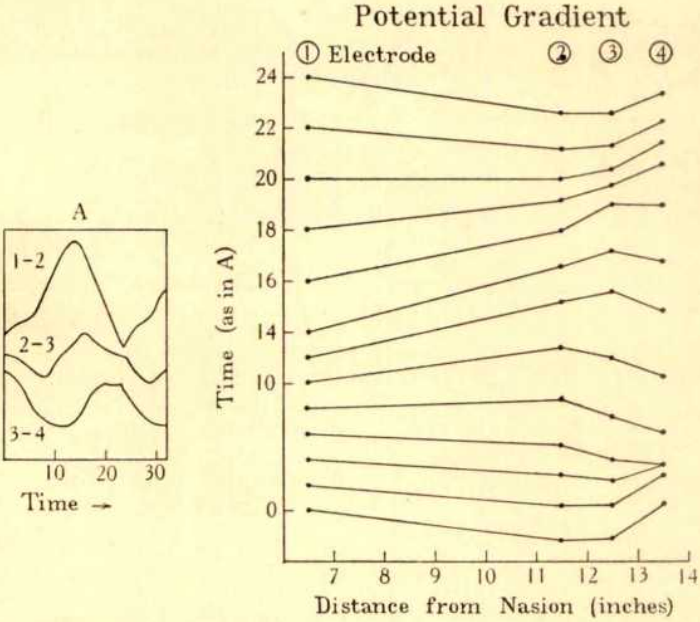

FIG. 26.—Potential gradients at different moments during a moving wave. Waves shown at A (record from K.Y). It is assumed that the potential remains constant at electrode I ($6\frac{1}{2}$ in. from nasion).

From records of this kind it is usually impossible to give more than a very rough estimate of the range of travel of the waves. In the back to front direction a movement of at least 1½ in. can certainly occur; we have no clear evidence of movement greater than 2½ in., but to be sure of its presence or absence would need simultaneous recording from many pairs of electrodes. In the lateral direction the range is much the same.

Moving waves appear more often in certain individuals: more in K.Y. than in E.D.A. and more in E.D.A. than in A.H. But it seems probable that some movement might always be found if we could map out the potential distribution in greater detail. Thus in K.Y. if one pair of electrodes happens to lie immediately over the focus of activity the potential gradient between these two electrodes usually undergoes a reversal in the course of a single beat, showing that the activity has begun near one of them and has moved over to the other before the beat has subsided. A pronounced shifting to and fro of the focus naturally affects the form of the waves recorded at more distant electrodes, making them rise and decline asymmetrically (*cf.* fig. 27). Whether movements of the focus account for all the irregularities in the wave form is another question, but clearly a great many can be explained in this way.

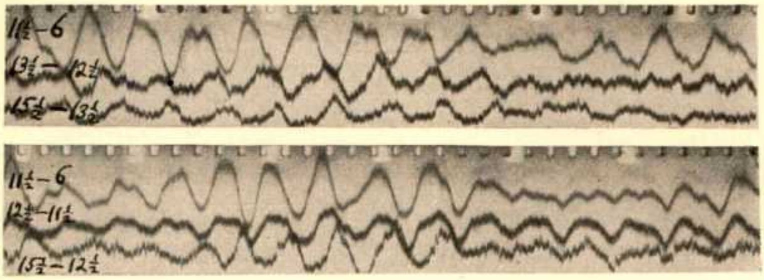

FIG. 27.—Record from K.Y., showing movement of focus and resulting asymmetry of waves.

We have, then, two distinct phenomena. The focus may move during each beat, the wave arising at one point and subsiding at another, and there may also be a shift, gradual or sudden, of the region in which the beat develops. Both kinds of movement might be expected in a region where all the units are ready to beat spontaneously and any of them may become the pacemaker. In fact the beats occurring in a fragment of the frog's auricle, or in a mass of embryonic heart muscle show much the same tendency to spread asymmetrically and to start now from one point and now from another.

ATTEMPTS TO CAUSE MOVEMENT OF THE FOCUS.

We have made various unsuccessful attempts to influence the position of the focus by producing activity in other parts of the brain. When the rhythm first appears after the eyes are shut the focus has shown no tendency to be in any particular part of the occipital area, and when the rhythm is abolished by opening the eyes the disappearance of the waves takes place without any significant change of focus. Again, there is no fixed tendency for the waves to appear or disappear sooner on one side of the head than on the other; we have made them disappear by unilateral stimulation, visual, tactile or auditory, but have found no clear difference in the records from the right and left occipital regions.

The only definite result has come from complex activities which reduce the size of the waves but do not completely abolish them

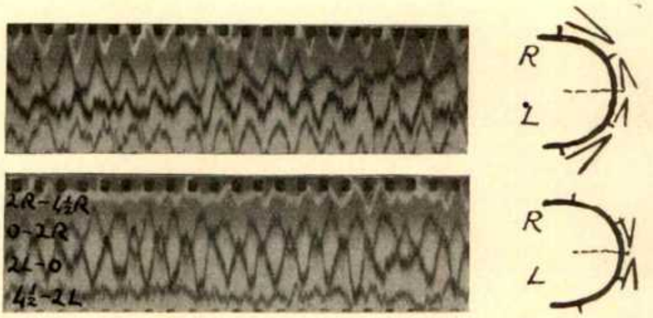

FIG. 28.—Reduction of active area by movement of focus towards the occipital pole during performance of a task needing great attention. Records from A.H. Above: normal, eyes closed. Below: writing alphabet with eyes closed. Electrodes arranged along horizontal circumference of head.

With these we have found a tendency for the active area to be confined to the neighbourhood of the mid-line instead of spreading out 2 in. or more laterally. An example of this is illustrated in fig. 28. The subject (A.H.) was asked to write down the letters of the alphabet, keeping his eyes shut. As often happens with an unfamiliar task, at the first trial the waves were completely abolished and at the third they were scarcely affected, but at the second they were much reduced in size and there was a shift of the focus towards the occipital pole. In two other individuals it has been possible to make the active region shrink towards the mid-line by imposing a task sufficiently engrossing to reduce the size of the waves. The nature of the task seems to be immaterial, for listening to and memorizing a string of numbers was as effective as writing the alphabet.

THE POSITION OF THE FOCUS DURING SLEEP.

Berger has shown that in deep sleep or in narcosis from various anæsthetics the potential waves are reduced in size and ultimately disappear. In these conditions some alteration of the focus might be expected. We have made records during sleep and have found no shift of the focus in the back to front direction. Unfortunately our records do not show whether there is any lateral shift.

The subject, A. H., prepared himself by going to bed very late and rising very early. The observations were made on two afternoons, and on both he slept so soundly that he could only be woken by a repeated sharp noise or by a vigorous shaking. When the subject lay awake with closed eyes the waves were almost continuous (fig. 29 A), in lighter sleep they occurred in groups (fig. 29 B) and during the periods of very deep sleep they were completely absent (fig. 29 C). As may be seen from the records the waves are always in phase from the three pairs of electrodes, i.e. over a region from 6 to 12 in. from the nasion. Waves recorded from electrodes at 12 and 14 in. from the nasion were opposed in phase to these whether the subject was awake or asleep. The focus therefore remains in its usual position as long as there are any waves to record.

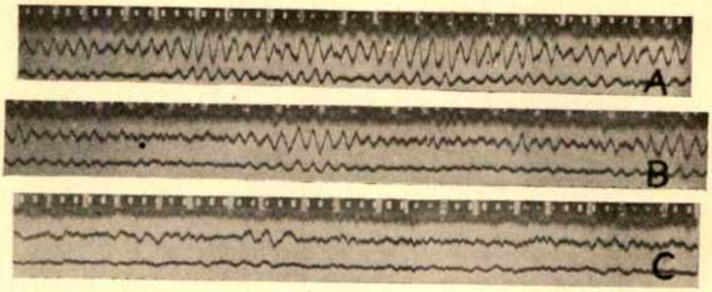

FIG. 29.—Failure of rhythm in deep sleep. Records from A.H. A, awake with eyes closed. B, light sleep. C, deep sleep. No alteration of focus.

A—Lowest oscillograph from electrodes at 12 and 10½ in. from nasion.
B—Middle oscillograph from electrodes at 10½ and 8½ in. from nasion.
C—Top oscillograph (scarcely visible) from electrodes at 8½ and 6 in. from nasion.

DISCUSSION.

The foregoing results show that the Berger rhythm may arise within a fairly large area of the cortex, but they leave no doubt that the main source of the potentials is in the occipital region. The focus is nearly always confined to the occipital lobe, i.e. to an area which might well be set free to beat spontaneously when the eyes are closed.

Within this area the focus wanders about in the seemingly haphazard way which might be expected of a beat due to a large collection of neurones working in unison. Opening the eyes should increase the activity in the occipital area, but the excitation would not be uniform, the neurones would be forced to work at different rates, and a sychronous beat would become impossible.

This conception of the rhythm has been discussed already by Adrian and Matthews and their arguments need not be repeated here, except to add that a non-uniform excitation might well involve a non-uniform inhibition of some of the units. This would, of course, contribute to the break up of the spontaneous beat. The alternative view that opening the eyes causes a direct inhibition of the whole active area cannot be altogether ruled out. It is possible, though very unlikely, that activity in the striate area might cause an inhibition over the rest of the occipital lobe. Published records from the exposed cortex in animals do not suggest that there is always an inhibited zone surrounding an excited striate area, but it is unsafe to argue from animals to man where vision is concerned.

As regards the effect of non-visual activities, we have no evidence to show whether the abolition of the rhythm caused by mental exertion differs in any way from the abolition caused by opening the eyes. Berger considers that both are due to the concentration of attention in a particular brain field with inhibition everywhere else. Adrian and Matthews regarded visual stimuli as falling in a special category since they can abolish the rhythm without making much claim on the attention. They suggested widespread non-uniform excitation as the cause of failure in non-visual activity, but admitted other possibilities. The present results leave the question still undecided.

There are, however, at least two cases where the abolition of the rhythm is almost certainly due to a diminished activity and not merely to a failure of synchronization. In deep sleep the rhythm disappears (fig. 29), and since all muscular tone and movement (save breathing) is absent, we may reasonably suppose that the cortical neurones have become less active. The failure of the rhythm in deep narcosis (found by Berger) must also be due to a genuine reduction in the activity of the cortex. Since in the case of sleep, there is no slowing of the rhythm before complete failure, it is probable that a small decrease of excitability is enough to prevent the development of the synchronous beat. It will be seen that two entirely different causes have been suggested to account for the failure of the rhythm, diminished activity during sleep and increased but non-uniform activity when the eyes are opened. Both suggestions rest on indirect evidence, but it is not unreasonable to suppose that there is a great difference in the state of the cortex in the two cases.

Since the potential gradients in the scalp are due, mainly at least, to potential changes in the occipital lobes, the failure of the rhythm must be due to a failure of these occipital potentials and not to a failure of potentials developed in other parts of the brain. There is, however, no reason to deny that other parts of the brain may contain groups of neurones which often beat at 10 a second. A frequency of this order is very commonly found in motor discharges and no doubt at any moment a large number of cortical neurones would be discharging at this rate.[1] But their activity would be inappreciable through the skull if they were scattered and not working synchronously in large enough groups. To give adequate potential changes the neurones must form a compact group covering an area several centimetres in diameter and working as a single unit. The neurones in the occipital lobe can behave in this way, but it seems that there is no other part of the brain in which so large an area can be freed from disturbing influences.

Since neurones may be forced to work synchronously by rhythmic stimuli we have tried to produce forced rhythms from other parts of the brain. But opening and closing the hand four times a second does not give potential waves of this frequency over the motor hand area and listening to a loud tick at 6 a second gives no corresponding rhythm over the temporal area. This lack of success is not surprising. The occipital area can be driven at different rates by a flickering visual field, but the rate and intensity must be very carefully adjusted and it is only with rates above 10 a second that the flicker rhythm appears without background disturbance. The areas involved in hand movement or in hearing are probably much smaller than that responding to flicker, and the procedures employed are less likely to induce definite rhythms. If rhythmic hand movements are carried out when the eyes are shut the frequency of the Berger rhythm is unchanged. Complex movements may cause a failure of the rhythm or a reduction of the active region, but there is no sign of any disturbance in the potential gradients in the region of the hand area.

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[1] There are several examples of a 10 a second rhythm from other parts of the cortex in abnormal circumstances. For instance, Dusser de Barenne finds regular waves at 10 a second from the motor cortex when the outer layers have been killed by thermo-coagulation, and a series of large waves at frequencies between 15 and 5 a second can be produced in almost any part of the rabbit's cortex by injury, electrical stimulation or convulsant drugs.

In every scalp record there are small, rapid oscillations of potential. These may be due in part to the cortex, but some are certainly muscle action currents and at present they seem to us to be too complex for analysis. Berger describes a definite series of small oscillations—the *b* waves—superimposed on the primary *a* waves of the 10 a second rhythm. The frequency of the *b* waves is given as 35 a second. We have been unable to detect them in our records, perhaps because we have not used needle electrodes in the scalp, but we have often found small inflections on the main wave suggesting that there are two regions beating not quite simultaneously (*cf.* fig. 27). These are usually found in records in which the focus moves to and fro during each beat. They may well be due to differences in the duration and rate of spread of the activity in different parts of the occipital area; they may, in fact, be comparable to the inflections which appear in the electric response of a beating heart. At all events, if they are due to a double instead of a single focus in each occipital lobe, the two foci must be linked in some way, for the inflections do not increase and decrease regularly as they would if the rhythms were independent.

In a conscious subject, therefore, the Berger rhythm is the only cortical potential change which we can clearly identify in a record from the scalp. Berger's recent work on epileptiform convulsions shows that the large potential waves which traverse the cortex can be readily detected through the skull, but these are products of an abnormal degree of synchronization. Their investigation will no doubt prove the most valuable outcome of Berger's discovery, for the occipital rhythm is disappointingly constant. The most interesting result which has emerged in the present work is that the focus of activity has a greater range of movement in some individuals than in others, though we have found no connection between the range of movement and any of the obvious physical[1] or mental characteristics of the individual. There are still many unsolved problems relating to the rhythm, e.g. the function of the neurones concerned, the effects of trying to see, the relative importance of pattern in the field and of attention to it, &c. It was not to be expected that a survey of the potential distribution would throw much light on these problems. But a detailed survey had to be made, for without it there could be no certainty as to the general nature of the waves.

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[1] The degree of development of the muscles and soft tissues at the back of the head is no doubt one factor which limits the apparent range of movement. An electrode on the neck muscles leads from an indefinite area on the base of the skull and its potential will be that of a point some distance forward from the inion. Thus the waves recorded from a pair of electrodes, one at 13 in. from the nasion and the other on the back of the neck, will be always opposite in phase to the waves from the top of the head, even though the focus is some way below the 13 in. point. In A.H. the soft tissues immediately below the inion are thicker than in K.Y. or E.D.A. and this may explain the limitation of movement of the focus downward, but it cannot explain the whole difference.

SUMMARY.

Adrian and Matthews have recently discussed the nature of the Berger rhythm, the potential oscillations in the scalp which take place when the eyes are closed. Their interpretation was based on the view that the waves arise in the occipital lobes from a region chiefly concerned with vision; Berger explains them differently since he considers that they are due to the whole cortex. The present experiments were made to obtain more exact evidence as to the place of origin of the waves. The potential distribution over the head was analysed by recording simultaneously with three or four pairs of electrodes on the scalp. It was found that the potential change reaches a maximum in the occipital region, the focus of activity on either side of the mid-line moving about within an area which extends laterally for 2 to 2½ in. and upwards from the inion for about 2 in. The range of movement varies with the individual.

By setting up an oscillating potential within the skull (in a cadaver) and recording from the scalp it was found that an active region on the surface of the cortex could be located to within an inch by the method in use. Inequalities in the resistance of the skull did not produce appreciable distortion of the potential distribution in the scalp. We conclude that the focus of activity of the Berger rhythm is in the occipital part of the cortex, though it is probable that the activity may sometimes extend beyond the margins of the occipital lobe.

Attempts to influence the position of the focus by activity in other parts of the brain have been mainly unsuccessful. The focus shifts from place to place in a way which agrees with the idea of a spontaneous beat arising within a large group of neurones, and in fact the results are consistent with the view of Adrian and Matthews that the rhythm is due to the synchronous activity of neurones which are left to themselves when the eyes are shut.

The failure of the rhythm when the eyes are open is presumably due to increased but asynchronous activity. But the rhythm may also fail from diminished activity of the cortex, as in very deep sleep or narcosis. Apart from the waves of the Berger rhythm and the occipital waves induced by a flickering field (Adrian and Matthews) we have

found no clear evidence of potential changes in the scalp due to the activity of the cortex. To give a reasonably large effect the neurones must act in unison over an area an inch or more in diameter. This can occur normally in the occipital lobe when the eyes are closed, but elsewhere it can only occur in conditions which favour an abnormal degree of synchronization, e.g. in epileptiform attacks.

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OBSERVATIONS ON THE TERMINATIONS OF CUTANEOUS NERVES.

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THE purpose of the investigations about to be described was to discover by means of section and anatomical investigation further support, if possible, for the theory that the elementary sensations of pain, heat, cold, and touch have a punctate distribution in the skin.

Our best thanks are due to Mr. A. McIndoe because he placed at our disposal his skill in cutting slices of skin at a thickness of about $\frac{1}{10}$ mm. To Dr. Carmichael we are also indebted because he carried out most of the sensory tests.

Before undertaking the present investigation we had practised for a considerable time the identification of cold spots on the volar aspect of the left forearm of one of us. This had gone on long enough to give us confidence that, once having identified a definite cold spot and marked it, subsequent retesting would elicit nearly every time the feeling of cold.

The various nerve endings which form the anatomical basis of punctate sensation occupy presumably some definite position in the skin. These, by our method of successive slices, would sooner or later be cut away. At the point where the ending was cut away there would lie the nerve-fibre which bore the ending. It was not clear what would happen on stimulation of the cut end of the nerve-fibre, but it has been assumed that its stimulation would lead to the same change in consciousness, that is the sensation would be the same as if the ending were present. On the other hand the threshold for the stimulus to excite the cut nerve fibre might be so high that no impulse would occur. The experiment of cutting off the ending might emphasize the importance of the ending for sensation, but would not throw much light on how it acted.

Other studies on the distribution of endings in the skin indicated that a fibre in the dermis might bear a large number of similar endings (over thirty coming from the same fibre have been counted) but these would be concentrated in a tiny area, less than that covered by the instrument for testing cold for instance. Other collaterals from the same fibre might perhaps extend outside the area of investigation. Theoretically such a possibility might complicate our interpretations.

If, however, cutting off the nerve ending did abolish the sensation evoked when normal skin was tested we might learn something about the anatomy of the removed ending, the position it usually occupied in the different layers of the skin, and at the same time find out, if the sensation were preserved, whether the experiment altered its punctate character. Finally, when the area was healed, testing and comparing the condition before and after operation would determine if the sensation returned to its original position.

METHODS.

We proposed first then to remove a succession of thin slices from an area of skin of which a map had been made by testing and marking the sensitive points. The area exposed after each slice was tested in the same manner as before, the stimuli being applied to the same points by superimposing the map of the sensory points obtained before the first operation. Each slice removed was marked in accordance with the map, and submitted to histological investigation. Then when all sensation except that of pain had been abolished the wound was allowed to heal, and when healed a map of its sensory points was compared with the original.

The outer side of the thigh was chosen as it is relatively poorly endowed with the different kinds of cutaneous sensation. Heat spots are rare, cold widely separated, but pain and touch are so close that, as elsewhere, it is not easy by mere spotting to be sure of their punctate distribution. Heat being the most difficult to investigate and no well-defined spot coming within our chosen area it was decided to omit it from the present investigation. A rough square was outlined, shaved, and tested.

For the identification of touch the finest von Frey hairs which would elicit the sensation with only slight bending were used. Five spots which responded definitely to this stimulus were marked.

Cold spots were identified by using a copper rod with a blunt point about 1 sq. mm. in area. When touched by this instrument the subject could distinguish the sensation of contact without any feeling of cold, the sensation of contact with a delayed feeling of cold, or cold which was felt at once as a flash when the rod was applied. The last was regarded as a cold spot. Three such were marked.

Pain spots were sought with the end of a needle and the four which gave the sharpest and most intense sensation were chosen.

The selected area was protected by gauze stuck down at edges with mastic and repeated tests were made to ensure the correctness of the marking. The results of the several tests were as follows :—

	Sensation	Number of tests	Successes	Failures
5	Touch spots	110	93	17
8	Cold spots	63	52	11
4	Pain spots	33	23	10

Frequently after testing the touch spots a sort of after image was experienced which lasted for about five seconds and felt as something crawling over the surface of the skin. The sensation of contact was best felt when the hair was applied and when it was withdrawn. Pain and cold spots gave no responses when touched with the hair. None of the pain or touch spots gave a sensation of cold when touched with the copper rod. Sometimes the application of the copper rod elicited the reply that the subject felt as though a cold bar had been placed on him and, when asked to point out the place where this was thought to be, he pointed to a region actually slightly distal to the area under observation. Pain was not elicited unless the needle was driven well into the epidermis.

Mr. McIndoe now proceeded to shave off a thin slice of the skin. This was done without any anæsthetic. The operation was painless except for an occasional sharp twinge from particular spots which it was possible to compare with our skin map. We agreed that there was close correspondence between the pain spots marked on the map and the exclamations denoting the experience of sharp pain. No other punctate sensation was aroused. The cutting of this slice might be described as painless except for the pricking sensations above alluded to.

The skin removed was divided into sizes suitable for examination by the gold chloride, silver and methylene blue methods. Blood oozed from many points on the exposed surface showing that the section had in places penetrated to the superficial layer of the dermis where the capillary plexus is situated. The slice was not uniform but was thicker towards the lower border and proximal margin. The cut was made from below upwards.

The histological examination of the slice of skin removed showed that the knife had removed the epidermis in part. In most areas the knife had passed through the deeper layers of the epidermis cutting across the apices of the papillæ in the corium. Towards the end of the cut the knife had gone deeper and the section included a fair amount of the capillary bed in the outer layers of the corium. The histological findings will be described later.

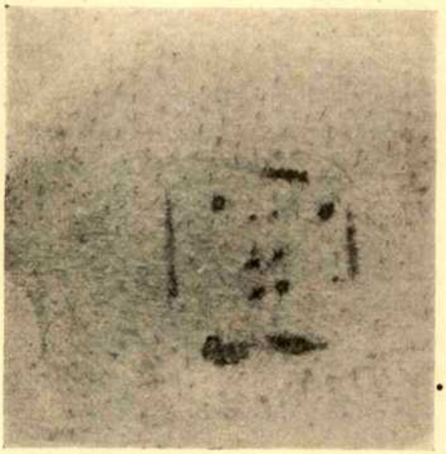

FIG. 1.—A photograph of the area mapped out before section.

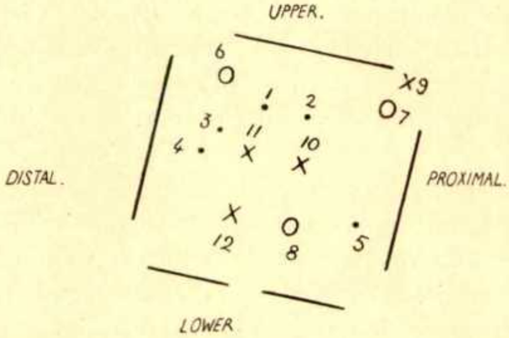

FIG. 2.—A sketch for the interpretation of the marked area on the thigh.

Touch marked by a • and numbered 1, 2, 3, 4, 5.
Cold ,, ,, o ,, ,, 6, 7, 8.
Pain ,, ,, x ,, ,, 9, 10, 11, 12.

THE DETAILS OF SUCCESSIVE TESTINGS AS THE SKIN WAS REMOVED.

The surface left by the first cut became covered with blood. This was mopped away and the area was immediately retested. By superimposing our map the points previously marked were readily identified.

These gave the same responses as before the cut, the only difference being that pain was more intense.

Twenty minutes later the raw area was again sliced through, Mr. McIndoe aiming to take off again a section about $\frac{1}{10}$ in. thick. This was done without an anæsthetic, but it was very much more painful than the first operation. There was, of course, more oozing, but it was possible after a short time to test the area which had been exposed. Twenty minutes after this second operation the area was again tested, using the map as before. No cold spots were found, pain was intense, but touch was elicited from the regions previously marked as tactile. Twenty-four hours later, the cold spots were now present in the upper part of the area (6 and 7, fig. 2), but the cold spot (8, fig. 2) in the lower part of the wound had disappeared. The touch spots and the places of most sharp pain were identified.

Another slice was now removed as before. The amount of oozing made immediate testing impracticable, but an hour after the operation it was attempted. Dr. Carmichael's examination of the wound enabled him to identify the touch spots, the points of most intense pain, and the two upper cold spots, but not the cold spot numbered 8 (*see* fig. 2). Three layers of skin had now been removed, and the knife was passing through the dermis except at the hair follicles and the longest papillæ.

A considerable amount of redness and œdema was present in and around the wound, and the pain felt on testing was severe. The next day the wound was again examined. The two spots (6 and 7) in the upper part of the wound were still present. Both in and around the wound searching for touch spots with von Frey's hair frequently caused pain, and it was hard to be certain of the presence of touch owing to this confusion. Some replies of touch were obtained, but localization was inaccurate. This was true not only for the wound, but also for the region adjacent to it. Pain was acute and experienced wherever pricked. It was not possible to bear it without flinching.

After marking the cold spots in the upper part of the wound and points where contact was experienced, the wound was again sliced under local anæsthesia. The exposed area was now well into the dermis, though islands of epithelium could still be found with a lens. On examining the wound the following day the two upper cold spots were again discovered. Being near the upper border of the wound they continued to escape owing to the surgeon being unwilling to extend the wound and tending to reduce the area of each cut. To some extent, however, they seemed to be changing their character, becoming more diffuse and losing their original precision. Touch could be felt, but by means of the lens it was discovered that it was experienced only where some portion of a hair follicle was present. Pain was felt everywhere, but in certain places it was more intense than elsewhere; it seemed to spread widely from the pricked spot.

A final slice was now made; the wound was deep enough to reach in many places the subcutaneous fat which could easily be seen.

The wound was deepest in the middle and towards the upper end. The upper cold spot (7, fig. 2,) was still identifiable. It had been missed by the knife. The second cold spot (6, fig. 2,) which had hitherto been recognizable was now gone. The detection of touch spots by means of the fine hair test succeeded at only one point. This was at a place where the knife had travelled less deeply and by means of the lens the remnant of a hair was found. The whole wound was very painful, but still there were places where by pricking points more painful than the rest could be found. Such points gave rise to pain so severe that it could not be borne without flinching. The experiment was now discontinued.

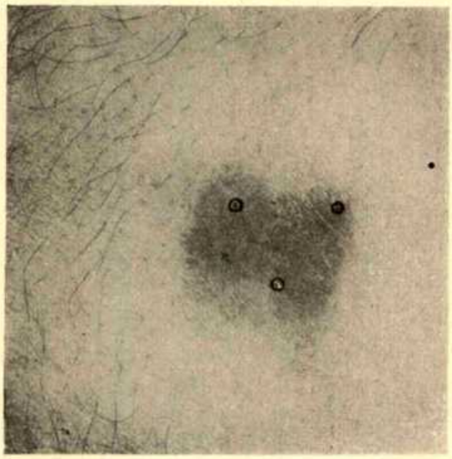

FIG. 3.—Photograph of the wound after healing is complete. The cold spots in particular have been brought out. When allowance is made for shrinkage in healing it is apparent that they correspond with the cold spots in fig. 1.

When the surface was healed the skin was again tested in the same manner as before. Particular attention was paid to the sensation of cold which previously had been abolished at two places. A photograph (fig. 3) is submitted on which touch and cold spots have been marked.

The three cold spots are prominently marked and it will be seen that they occupy much the same positions as before, and if allowance is made for the contraction occurring during the healing of the wound the identity of position is established.

Since the primary object of the experiment was to obtain information about the anatomy of nerve-endings it is not proposed to discuss in detail observations which do not bear directly on this aspect.

This simple experiment was beset with many difficulties. It was not possible to cut the sections of the same size and thickness, and the shelving edge of the wound led to the preservation of nerve endings near the margin. The oozing, the pain, the coagulation on the surface of the wound, and the need for an anæsthetic made immediate testing, except after the first slice, difficult, uncertain, or impossible.

The immediate effect of cutting caused confusion of the various sensations. The perception of cold was immediately lost, but after a period, not exactly determined, the ability to appreciate the various sensations returned.

The increasing intensity of pain was striking. It seemed to increase with each successive slice, and it was not possible to refrain from reflex withdrawal. The work of others suggests that this phenomenon is not primarily anatomical. The spreading of the sensation from places where intense pain was elicited made it very difficult to be certain of the state of other forms of sensation.

The preservation of touch in the hair follicles is of interest since it seems to have been retained when only a portion of the usual innervation of the follicle itself could have been present. After the last operation it was possible to find touch only in places where it was possible to find a hair follicle.

One cold spot ending disappeared early in the experiment. Stimulating this spot with the copper point even after it had been placed in ice did not arouse the sensation of cold. As other cold spots within the area remained sensitive though subjected to some of the effects of the trauma the absence of response from this spot was in all probability due to the cutting-off of the ending itself. Such an experiment does not help in deciding the way in which an ending may act—whether the action is due to change in the threshold value or the production of a chemical substance. It does, however, emphasize that the ending is an important part of the mechanism, something more perhaps than a mere increase of neural surface.

From the order of the disappearance of the different sensations in the course of these experiments it is to be inferred that pain is at once the most superficial and the most extended through the various cutaneous strata. Superficial touch persists after the removal of the most superficial part of the epidermis, but disappears as the cut goes deeper. At about the same level lies the cold ending. Touch is carried deeper into the tissues by means of the hair follicle. We have no observations on heat spots.

The presentation of a punctate distribution throughout the experiment, the subsequent return to the original position, and the possibility of abolishing one point in a series of similar sensory points, adds additional weight to the theory of the punctate distribution of sensation, and in consequence to the notion that each form of sensation has its own anatomical form.

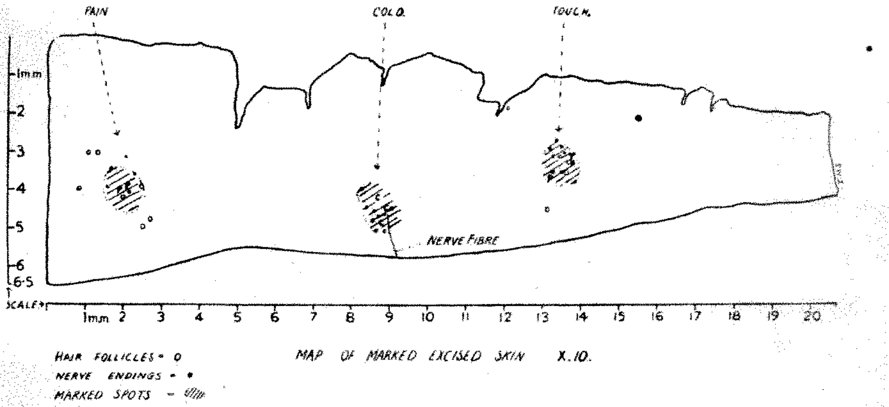

FIG. 4.—A sketch of the excised portion of skin enlarged 10 times. The sketch shows the marked points and other nerve endings and hair follicles observed plotted in their relative positions.

HISTOLOGICAL SECTION.

We had hoped, despite the lack of success attending similar investigations hitherto, to be able to determine the anatomy of each sensory point identified at the level of each section. Previous investigations of this kind had broken down mainly owing to the technical difficulties of histology. We were also to be disappointed for our preparations made with gold and silver gave us only bits and scraps of nerve-fibres that could not be interpreted. However, the supravital staining with methylene blue was much better, and in so far as we could use extensive portions of the skin removed, interpretation, though difficult, was not impossible. Unfortunately the reactions occurring in the wound soon made this kind of staining impracticable, and it is only possible to rely on the earliest sections.

Of the various sections prepared in different ways and made from the different slices, that which was stained in methylene blue and came from the first slice was the most interesting. This slice was stained by immersion in methylene blue. The surface exposed by its removal oozed at various points. Thus the section had cut through the papillæ of the dermis in places leaving the deeper layers of the epithelium adjacent to these.

Fig. 4 is a sketch of the piece of skin as it appeared when stained with methylene blue. It is drawn to scale and on it are marked the places from which the sensations of pain, cold and touch were obtained. In addition, there are recorded also hair follicles and nerve fibres and endings which were discovered apart from the actual marked spots.

Pain Fibres.

In the region of the spot marked as the place where pain of a sharp and intense character was elicited there were found in amongst the epithelial cells of the epidermis an irregular plexus of fine beaded fibres. The fibres were extremely fine and had varicose outlines. The irregular outline is due in the main to the fact that the fibres are travelling to and fro between the adjacent margins of the epithelial cells. Sometimes the ends take the form of fine beads which grow finer and finer until they pass beyond the range of visibility. In other places the ends have the form of tiny knot-like expansions. As the fibre approaches the epithelium it appears to be a little thicker, but gradually as it subdivides and gives off branches it becomes thinner. These fibres in the epidermis come from a subepithelial plexus which ramifies in a complex manner and here and there sends its branches up into the epidermis. The method of preparation is not suitable for determining the finer points of relationship to the epidermal cells. It cannot be determined for instance whether the ultimate ends are actually situated within the cells or outside them. Kadanoff has described two kinds of nerve fibres entering the epithelium, a thicker fibre which gives off lateral branches and a thinner one which remains unbranched. He is inclined to suppose that these differences are of functional significance. Kadanoff relied upon silver preparations, but neither this nor any of the other methods available are particularly reliable for the determination of such points. Methylene blue is no worse and perhaps even better for the resolution of such problems as the thickness of axis cylinders and neurofibrils. However, these observations have not demonstrated any differences between these intra-epidermal fibres.

The allocation of pain to these fine varicose fibres wandering amongst the epidermal cells is agreeable on many grounds. The observations of v. Frey on the cornea are cited in every textbook. There are the results of the investigations of Ranson and of Adrian and others that pain fibres are amongst the smallest of nerve fibres and have their own rate of conduction, change of potential, &c.

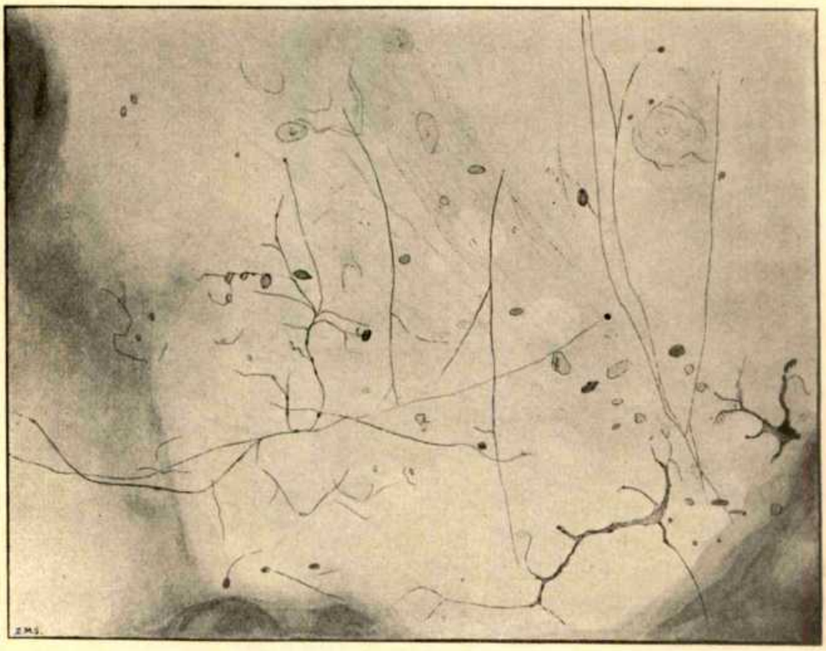

FIG. 5.—Drawing of fine plexus of nerve fibres in the area marked for pain. A few blood corpuscles are included and also the opening of a hair follicle. In the bottom right hand corner two branching cells (cells of Langerhans) have been drawn.

The present observations support these contentions in two ways. The fibres have the situation and the morphology generally attributed to pain fibres. They occur in a situation which when tested prior to removal responded with sharp intense pain, i.e., they occur at the place so marked. When the cut was made without any anæsthetic the advance of the knife was easily borne, a sharp pain being felt only when the knife was passing through the spots marked to indicate the places where sharp pain could be elicited by the prick of a needle.

The method we have used has certain drawbacks. The area necessarily undergoes shrinking in the course of fixation. Further it is a flat thin slice and in addition is pressed flat in order to make it easier to examine with the higher powers of the microscope. For these reasons it is not easy to decide to what level these intra-epidermal fibres extend in the epidermis. When, however, we compare these fibres with similar ones which we have found in other preparations we are of the opinion that they extend through the inner two-thirds of the epidermis.

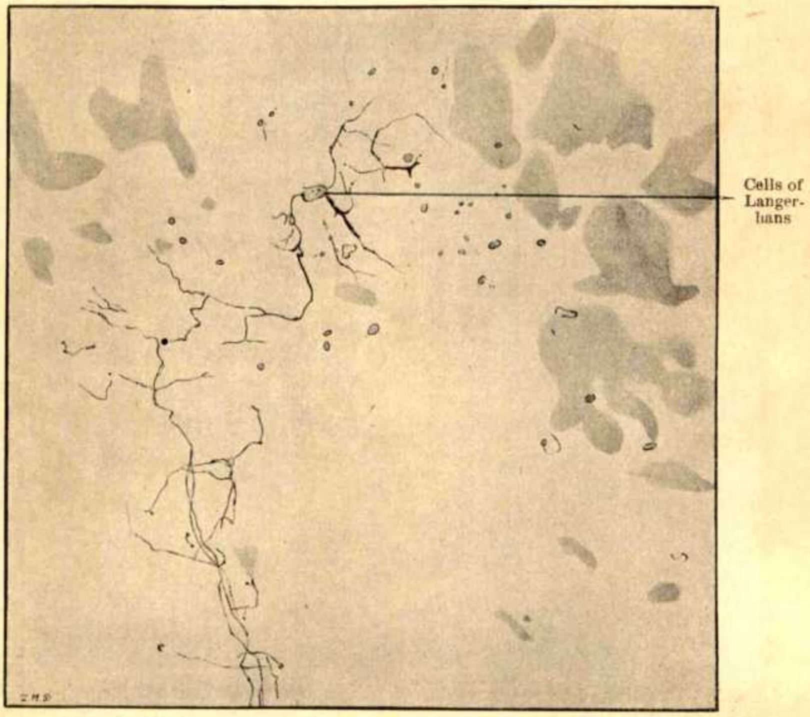

FIG. 6.—Another drawing of the same plexus as shown in fig. 5. The ramifications of the fine beaded fibres of the pain plexus are shown together with some branching cells and the ink marks in dark grey.

The investigations of Waterston have led him to conclude that the fibres most superficial in the skin are touch fibres. The fibres illustrated in his paper seem to be the same as are described here as pain fibres.

It will be noticed in the photomicrographs and drawings that large branching stained cells are present. These are constantly found in the deepest layers of the epidermis with methylene blue staining. They have, of course, been variously designated and interpreted in the course of histological study of the skin. They have come down to us as the

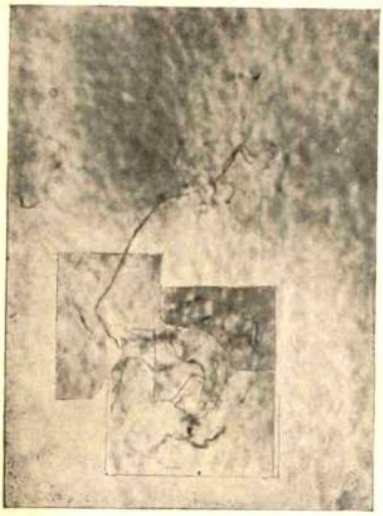

FIG. 10A.

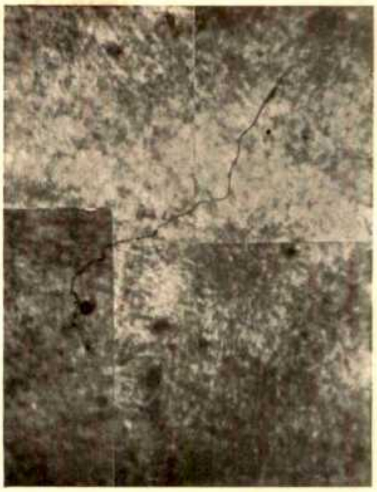

FIG. 7.

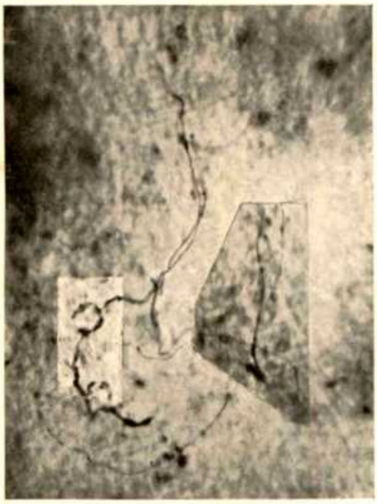

FIG. 10B.

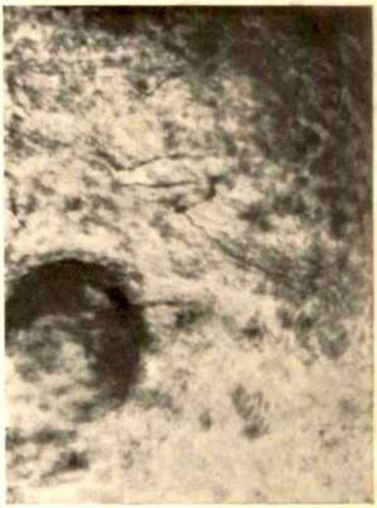

FIG. 12.

FIG. 7.—A photomicrograph of a fine beaded nerve in the deeper layers of the epidermis in the region marked for pain. The photograph has been obtained by piecing together several pictures taken separately because of the changing level of the nerve. The dark mass below is a portion of the ink mark made to identify the place. Enlargement 500 times.

FIG. 10.—Photomicrographs A and B of the endings and fibres found in the region of the spot marked as cold. The black areas represent the marks. The nerves and ends were photographed through the overlying epithelium. The photographs have been built up from several pictures because of the differences in focus. Enlargement 500 times.

FIG. 12.—A photomicrograph of the follicle and nerve fibres found in the region marked as touch. Enlargement 500 times.

To illustrate paper by H. H. Woollard.

cells of Langerhans. It seems quite clear that they have nothing whatever to do with the innervation of the skin and this is the most common opinion about them. They bear no constant relation to nerve fibres and nerve fibres do not end upon them. Though they have been regarded as nerve cells and their processes as nerve fibres they are in all probability pigment cells.

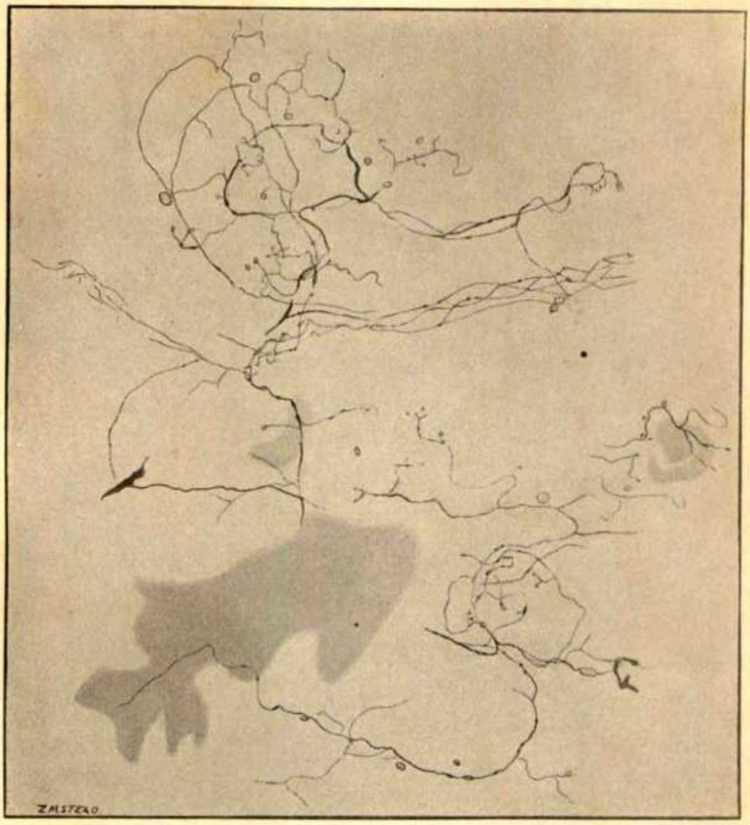

FIG. 8.—Drawing of nerve fibres and endings found in the vicinity of a spot marked as cold. The gray areas are portions of the ink marking.

COLD SPOTS.

The middle spot of the excised piece of skin (*see* fig. 4) was marked as a place from which a sharp response of cold was obtained by means of touching the spot with the end of a copper rod. Immediately in the vicinity of this spot there is a complicated nerve plexus lying subjacent to the epithelium and just above the loops of the capillaries. This plexus is formed of fibres of moderate thickness which branch and subdivide in a diffuse manner. The terminations take the form of expansions of considerable size, sometimes elongated and sometimes ovoid. The ends are non-encapsulated though they lie close enough together to give the impression of a well-localized ending.

Our method of marking our spots was somewhat crude and covered a larger area than was desirable or necessary. Nevertheless we have found in the vicinity of a place marked as definitely responding to cold a nerve fibre and ending of special character and special situation. Furthermore, we have encountered similar fibres and endings in normal preparations and have been able to study them in greater detail. Because of the presence of similar ends in other parts of the skin we propose to suggest that these are the anatomical basis of the sensation of cold. The ending is subepidermal and, unlike a Meissner corpuscle, is not elongated into a climbing compressed spiral ending. The clustering

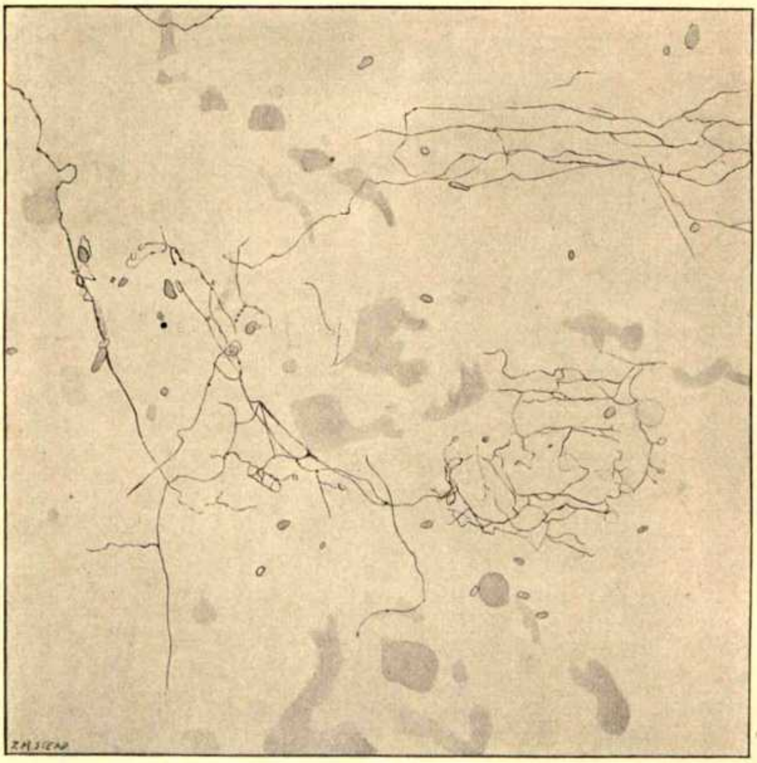

FIG. 9.—Another drawing of the endings and nerve fibres in the vicinity of the spot marked as cold. The gray splashes indicate the ink marks.

discs which form the ending are attached on tendrils that give to the whole expansion a complex interlacing and diffuse character.

In 1886 Goldschieder carried out similar experiments to the above and under the places marked for cold he too found a distinct subepidermal plexus which is very probably the same sort of thing as we have just described. Goldschieder preferred, however, to discuss his findings in a more general way and regarded such plexuses as underlying a temperature sense and having a special relation to blood-vessels. The methods of impregnation of nerve fibres and endings available to Goldschieder were not so good as those now in use.

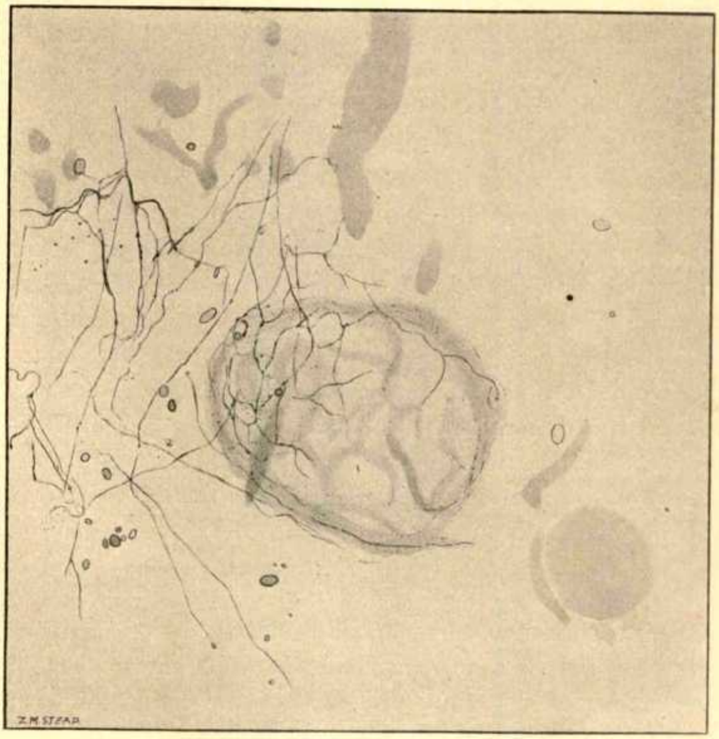

FIG. 11.—Drawing of the hair follicle and its innervation found in the vicinity of the region marked as touch.

Various suggestions have been put forward as regards the anatomy of the cold spots. v. Frey has suggested that the genital corpuscles may function as such. This may be, but it does not help in the present study, for these bodies are not found in the extragenital places of the skin. He has also suggested that certain end aborizations described by Ruffini may also function as cold receptors. It is not unlikely that the ends we have been describing are of the same order. In the maze of descriptive anatomy of nerve endings it is difficult to be certain about the identification of one description with another. Strughold and Kärbe found terminals in the margin of the conjunctiva which are not dissimilar from those described here, and these they identified with cold. Belonoschkin marked out the cold spots on the skin of the mammary gland. After this had been removed by the surgeon he studied by modern silver methods the anatomy of the endings in the vicinity of his marked cold spots and, attributed to cold, an ending which was non-encapsuled and which was situated about $\frac{1}{10}$ to 2 mm. below the epidermis. This agrees well enough with the present results.

TOUCH SPOT.

In the area which was shown in fig. 4 there was one point marked as a site where touch was elicited by the finest hair test. In the stained section it was discovered there was a hair follicle which previously was not seen by use of the lens. On this in the usual palisade manner of investment an encirling nerve fibre was discovered. By common consent the hairs, especially the fine ones, are refined organs of touch.

Reference has been made in the text of this paper to the parts played by Mr. A. McIndoe and Dr. A. Carmichael. I am grateful to them for their co-operation. I wish to thank my assistant, Miss Stead, who has helped me in all parts of this investigation and made the drawings which illustrate the results obtained.

SUMMARY.

(1) Our investigations furnish additional evidence for the punctate theory of sensation in that successive slices of the epidermis and the dermis as far as the subcutaneous fat show at each section spots from which a special sensation can be elicited. After regeneration the spots recur in the same position.

(2) So long as the ending is present its special receptor quality can be elicited.

(3) A fragment of the ending can still exhibit the special receptor quality.

(4) The special quality may be annulled immediately after section of the skin (cold), but if the ending is still present its quality returns after a time.

(5) When the ending is cut away the nerve fibre cannot be aroused by the original stimulus, even when this is intensified.

(6) Evidence has been furnished as to the existence of special ending for cold. The result is in good agreement with the results of other observers.

(7) In general it may be put forward that pain, cold and touch have characteristic position, fibres and ends.

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CHRONIC PROGRESSIVE (ENDOTOXIC) POLYNEURITIS.

BY WILFRED HARRIS.

ACUTE polyneuritis is one of the commonest diseases of the nervous system, but a slowly progressive polyneuritis not due to any obvious cause such as lead or alcohol, and in which the development of the symptoms is spread over many months, or even years, is as rare as the acute form is common.

A recent case which has been under my care, and in which the symptoms slowly progressed and continued for five years until death from respiratory paralysis, prompts me to review the whole position of the chronic forms of polyneuritis.

In an article on "Toxic Polyneuritis" in 1922 [3] I described two cases under the description Slow Chronic Polyneuritis, in both of which the symptoms developed progressively for about twelve months.

Case 1.—A man, aged 31. There was very considerable atrophy of the limb muscles with contractures seventeen months after the onset, and anæsthesia of peripheral type. The upper limbs were not involved until the legs were completely paralysed, nine months after the commencement of the disease. No source of toxæmia could be discovered.

Case 2.—A girl, aged 15, whom I saw in August, 1912, when all four limbs became completely paralysed. The neck muscles also became gradually involved, so that she could not raise the head from the pillow, the eyelids and lips were also partially paralysed, and there was weakness of mastication and the tongue also wasted partially. In her case there were never any sensory symptoms beyond slight paræsthesiæ of the finger tips at the commencement, and some tenderness of the calves and forearm. To electrical tests, no faradic reactions obtained in any muscle of upper or lower limbs. To galvanism, feeble reactions were obtained in the thighs and arms, more marked and sluggish in the forearms, with full reaction of degeneration. She was put on treatment by massage and galvanic reversals of current twice daily, and after two months' treatment the faradic reactions were returning in all the muscles of all extremities. Wave faradism was now substituted for the galvanic current. In spite of the improving electrical reactions, the muscles continued to waste and she became weaker in the neck and in power of sitting up. There was now some difficulty in swallowing, and occasional choking, and there was obvious atrophy of the tongue, while the weakness of the sphincter muscles of the eyes and lips gave the facies rather a myasthenic appearance. None of the muscles, however, gave the myasthenic reaction on tetanizing by prolonged faradization, and she was always better and brighter in the evening than after a night's sleep. After eighteen months from the commencement, she began to improve, and gradual recovery became complete after another two years.

I have had under my personal care three other cases of an unusual type, which might be classed with these.

Case 3.—One is a girl now aged 23, who is at present recovering from her third attack of polyneuritis in six years. When aged 17, in March, 1929, she kept her bed for one day on account of slight pyrexia and headache. Six weeks later she noticed weakness of the hands and arms, which ten days later also affected the legs. The weakness became general, increasing in all four limbs and in the trunk muscles until June 11, when she began to improve. When admitted to the Maida Vale Hospital on June 21, 1929, she could walk only with support and could scarcely lift her arms and was unable to feed herself. The neck muscles and all the cranial nerves were unaffected, and respiration and the sphincters were normal. All the deep reflexes were lost and the limbs were hypotonic; the abdominal reflexes brisk and the plantars flexor. There were no sensory symptoms of any kind, neither pain, paræsthesiæ, tenderness, nor any anæsthesia. She improved steadily, leaving the hospital in September, and she continued to improve until three days after Christmas 1929, when her limbs suddenly gave way and she fell, and was unable to get up. The weakness increased rapidly and she was readmitted to hospital on January 18, 1930. There was then complete paralysis of all muscles of the arms and legs, though respiration, and the muscles of the head and neck and cranial nerves were normal. There was no spontaneous pain nor any trace of anæsthesia, but there was tenderness of the calves. The deep reflexes remained absent, and the muscles reacted only poorly to the faradic current. The paralysis remained practically unaltered for months, though she had to leave the hospital at the end of April for some weeks owing to an attack of varicella. A note taken on December 9, 1930, states that there was complete wrist and foot drop, and inability to abduct the arms, and that she was unable to extend the knees or to stand. Improvement was extremely slow, and on this occasion she was in the hospital for two and a half years until June, 1932. Ultimately her recovery was complete and for over two years she was perfectly well and able to do everything and to play tennis. In November, 1934, she caught a cold in the head, and a week later her left arm became weak, then the right arm, and the legs shortly afterwards. She then came under the care of Dr. Blake Pritchard, both at the Maida Vale Hospital, and in the University College Hospital under Dr. Walshe, and I am much indebted to them for permission to use the notes of her condition in this third attack. On this occasion pain developed two months later in January, lasting for a month, her fingers and wrist feeling "as though being broken." There was never any pain in the legs, though tenderness in the calves and forearms developed, and is still present (June 22, 1935). She is still unable to lift her arms and cannot move her ankles or toes. A point of some interest, in view of the good effect of prostigmin in myasthenia, is that an injection of this drug was of no benefit, and made her feel definitely ill. There is no trace of any sensory loss, and the deep reflexes are all absent. No enlargement of any nerves can be felt.

This case might justly be classed as both relapsing and recurrent. Though in her first attack the weakness gradually increased for three months, in her second attack the onset was acute, almost sudden, and in her third attack, after an interval of perfect health for two and a half years, the paralysis again developed within a few weeks. The case differs, therefore, in certain details from the slow chronic or progressive form of polyneuritis, in which the symptoms develop gradually over many months or even years, though it will be observed on comparing the accounts of different cases that a symptom absent in many, such as pain, may be present in some, as in my first case of a man, aged 31 [3], and in the third attack in Case 3.

Case 4.—I published with Newcomb in 1929 [4] a case of relapsing interstitial hypertrophic neuritis; the man, aged 52, had six separate attacks of paralysis during six years, and a final one commencing a year later and progressive to a fatal ending in fifteen months. In his case there was never any pain or sensory symptoms, and the paralysis never became universal before death, though there was full reaction of degeneration in the leg and forearm muscles. He had in previous attacks had slight choking seizures, and at the end he was seized with severe choking, rapid pulse and respiration, indicating involvement of the bulbar nerves. During life there had been no suspicion of any hypertrophy of the nerves, though these were found enormously hypertrophied, with demyelination of the motor fibres particularly and great proliferation of the sheaths of Schwann and the presence of numerous "onion bulbs" as in the Dejerine type of case.

My fifth case was steadily progressive for five years until death from increasing respiratory distress and choking.

Case 5.—A man, aged 34, had an accidental fall, cutting the back of his head and damaging his right ankle. From that day his right leg has been weak and has got gradually weaker ever since, the left leg becoming weak nine months later. He was seen in Durham by Dr. Nattrass, of Newcastle, in October, 1931, who has kindly lent me his notes of the case. There was then no pain or numbness, and no symptoms referable to the upper limbs. He had a waddling, rolling gait, with double drop foot; the thigh muscles were extremely atrophied, especially the right quadriceps, and the muscles below the knees were also notably wasted, with the power much diminished. The knee and ankle jerks were much diminished, especially on the right side, the plantars flexor. There was no trace of any sensory loss, or sphincter weakness, and the upper limbs and cranial nerves were quite normal. Though there was no family history of any similar affection, the diagnosis at that time appeared to indicate a distal type of muscular dystrophy. His weakness steadily progressed, and in April, 1933, he nearly died of bronchopneumonia. He afterwards put on fat to the extent of 30 lb. in weight, but for the four months before I saw him on January 25, 1935, he had been complaining of increasing dyspnœa. He was carried about pick-a-back by his male attendant.

On examination on January 25, 1935, there was total flaccid paralysis of all muscles of both lower limbs, trunk and abdomen and intercostals. Diaphragm good. The only movements possible in the arms were slight extension of the index fingers, no power of movement of shoulders. Wasting of all intrinsic hand muscles of both hands. Complete paralysis of the retractors of the head, which falls forward. Flexion of neck good. All cranial nerves normal. All deep reflexes, plantars, and abdominals absent. No sensory changes of any kind; no pain or tenderness. To electrical testing, some contraction to faradism in the extensors of the fingers, but complete reaction of degeneration, with large sluggish contractions to galvanism in the rest of the extensors, biceps and deltoids on both sides. No faradic excitability of any lower limb muscles, with weak sluggish contractions to strong galvanic shocks of 20 to 25 milliamps. No enlargement of nerves could be felt. Treatment ordered: injections of strychnine twice daily, massage, and galvanic treatment to the muscles. On April 5 he was definitely improving in muscular power, he could then extend the left wrist and both thumbs, and could contract the left deltoid. The voice was stronger, and there was better control of the neck muscles. Early in May he began to have slight difficulty in swallowing, and a tendency to choke. This increased rapidly in the second week of May, and he died May 15. No autopsy was permitted.

This case in many respects bears a close resemblance to that of Case 2 in the universal paralysis of limbs and trunk with practically complete absence of sensory symptoms. Both developed choking attacks late in the course of the illness, but the man's case was slower in development and ended fatally. No source of toxæmia was discovered in either case, and it seems certain that neither was due to absorption of any external poison, but must have been dependent on some form of endotoxin.

Case 5 in some respects resembled Case 4. Physically the two men were somewhat similar, and in neither could any enlargement of nerves be felt during life. Unfortunately I was unable to examine the nerves of Case 5 after death, but I should not have been surprised if they showed similar changes to those in Case 4. The clinical courses varied, six separate attacks of partial paralysis, with intervening recovery, occurring in Case 4 during six years, the last being fatal, with choking attacks, much as in Case 5, though there were no intermissions in the latter's illness. The presence or absence of intermissions does not appear to me an essential feature distinguishing the recurrent form from chronic progressive polyneuritis. My Case 3 is now recovering from her third attack in six years, and such recurrence, in the absence of external toxins, would indicate a variation in the activity or development of any endotoxin rather than any essential difference between the recurrent and steadily progressive forms. In my Case 2, a girl aged 15, though her illness was slowly progressive for over twelve months, yet she ultimately made a perfect recovery, and remained well at the age of 31 except for the development of pulmonary tuberculosis, following typhoid fever. For the first twelve months of her illness her case resembled in many respects that of Case 5, though his was even slower in development, and showed only slight signs of improvement before the fatal bulbar development. In her case the arms were first affected, while in that of the man the legs became severely paralysed and wasted many months before the arms became involved. She also, when at the worst stage of her illness, developed some difficulty in swallowing and attacks of choking, as in the two fatal cases, Cases 4 and 5. In her case only was there any involvement of cranial nerves, definite weakness of some of the facial muscles, as well as atrophy of the tongue being observed.

J. Schlier [8], in an article on "Recurrent Polyneuritis," describes a case under this diagnosis which is clearly not a polyneuritis but a typical example of the relapsing variety of disseminated sclerosis. His case was that of a young married woman, aged 29, who developed weakness and almost complete paralysis, left retrobulbar neuritis with blindness, external rectus palsy, left increased knee-jerk and bilateral ankle clonus. Temporary improvement was followed by seven recurrent attacks in six years.

In an excellent article on "Recurrent Polyneuritis" Sorgo [10] gives an account of a case with autopsy. He objects to the term recurring polyneuritis when the attacks recur at long intervals of complete health, and so would not include Targowla's [11] case who had three attacks when aged 19, 27 and 39. The same argument applies to Thomson's [13] case of two attacks at 5 and 19, whose second attack of paralysis followed five days after being immersed in cold water, the paralysis being general in all four limbs, with facial diplegia, ten days later. Complete recovery occurred within two years, but the rapid onset of the second paralysis after a chill lends support to Mary Sherwood's [9] suggestion that the first attack of neuritis leaves the nerves with a lowered power of resistance to a fresh toxæmia. The same reasoning explains the liability in a case of lead poisoning to recurrence of wrist-drop from some slight cause, as a febrile attack or an irregularity in diet. Sorgo's case of recurrent polyneuritis is the first to be published with account of autopsy. His case was a man, aged 58, who after three attacks of abdominal pain and constipation developed polyneuritis with recurrences after intervals of five and three months, the last being a more severe attack, ending in respiratory paralysis and death. The whole illness covered twenty-two months. Degenerative neuritis was found in the peripheral nerves.

Both in this case and in that of H. M. Thomas [12], whose patient had five attacks of paralysis within six years, indigestion and abdominal pain was a feature of the illness before the development of the neuritis, and diarrhœa was a prominent symptom in the three fatal cases referred to by de Bruyn and Ruby Stern [1]. Compare also the abdominal pain and obstinate constipation associated with hæmatoporphyrinuric polyneuritis (see *Brain*, 1922, 45, pp. 429-432). The coincidence of abdominal trouble, pains, constipation or diarrhœa, preceding the development of polyneuritis is strongly suggestive of an enterotoxin being the cause.

Hyland and Ritchie Russell [5] describe a fatal case of chronic progressive polyneuritis, and I accept this nomenclature as preferable to slow chronic. They refer only briefly to Sorgo's case, with no description of its onset or progress, and the bibliographic reference is faulty. Their case was steadily progressive for twelve months, and died with respiratory failure and choking attacks, which seems to be the characteristic ending of the fatal progressive cases. The nerves of the upper extremity were larger than normal, and pinkish in colour, and microscopic examination showed degeneration of the myelin and proliferation of the sheaths of Schwann, in the anterior roots and peripheral nerves, with increase of the connective tissue, but no onion bulbs. The sensory roots and nerves were much less affected, and the spinal cord showed no tract sclerosis, but some shrinking of anterior horn cells. No cause for the illness was suggested, beyond the occurrence of a rash on the left side of the head and neck for several weeks about the same time as the commencement of the weakness. Hyland and Ritchie Russell suggest that their case is of the same type as my Cases 1 and 2, which recovered, with which I agree, but I would also include the case which I published with Newcomb [4] in 1929 as a case of relapsing interstitial hypertrophic polyneuritis, and also de Bruyn and Ruby Stern's [1] cases, inasmuch as I am not inclined to look on the neural hypertrophy as an essential feature, as some nerve enlargement was present in Hyland and Ritchie's case just referred to, and also in Nattrass's case [6] in 1921, which would clearly belong to this group, although no biopsy or autopsy was available in the latter.

The fact that enlargement of the nerve trunks, due to proliferation of the sheaths of Schwann and the interstitial tissue, has been found in certain cases of chronic progressive polyneuritis, such as my Case 4, does not appear to me of sufficient importance to justify their separation, as a distinct group of hypertrophic neuritis, from cases such as my Cases 1, 2, 3 and 5. No biopsy was done in either of these cases, and it is certain that many nerves may be much enlarged and escape observation during life.

The type described by Dejerine and Sottas [2] is frequently juvenile and familial; it is slowly progressive for years, with talipes equinovarus, and often kyphoscoliosis, usually severe pains with peripheral anæsthesia and much wasting, often closely resembling the peroneal type of atrophy of Charcot-Marie-Tooth, and always accompanied by posterior spinal sclerosis.

Ritchie Russell and Garland describe seven cases of progressive hypertrophic polyneuritis [7] which clearly are of the same type as those of Dejerine and Sottas, showing familial tendency, pes cavus and kyphoscoliosis, nystagmus, ataxy, and enlargement of nerve trunks. Although slowly progressive for many years there is little fatal tendency in these cases, and probably posterior spinal sclerosis would be found on examination, as in all cases of the Dejerine type.

Many cases of muscular atrophy of the Charcot-Marie-Tooth variety have been shown to have sensory changes of the glove and stocking type, and posterior spinal sclerosis has also been demonstrated many times. Moreover, in the late stages of Friedreich's hereditary ataxia it is well known that anæsthesia of peripheral type as well as considerable muscular atrophy may occur. Thus the progressive hypertrophic neuritis of Dejerine-Sottas, which is essentially familial, and often commencing in childhood, shows a definite relationship to the Charcot-Marie-Tooth atrophy on the one hand, and on the other to the familial hereditary ataxias, and all may be classed amongst the abiotrophies, or diseases of congenital mal-development.

Of the three cases described by de Bruyn and Ruby Stern as belonging to the Dejerine-Sottas type, although familial, the only case they examined showed during life no nystagmus and no deformities, and there was almost complete absence of posterior spinal sclerosis. Their diagnosis rests practically on the presence of hypertrophic neuritis, showing changes similar to those found in the Dejerine type. Yet these three cases all ran their course to a fatal end within three years, severe diarrhœa being a prominent symptom. This history is suggestive of some subacute toxæmia, perhaps an endotoxin, and I consider they should be classed with my five cases as chronic progressive polyneuritis. The neural hypertrophy in these and my Case 4 and others, should, I consider, be looked on as of minor importance, and as one of the secondary effects of the neurotoxin causing the disease. In some of the cases temporary improvement or complete recovery may be succeeded by recurrent attacks at varying intervals of months or years, while another, as my Case 2, may recover after two or three years and never again suffer, and yet another, as my Case 4, may have numerous recurrent attacks and then succumb with bulbar symptoms, and another, as my Case 5, may be slowly progressive for five years, with no intermissions, and then perish with bulbar neural paralysis.

Though varying in detail, the common features of a slowly progressive motor paralysis, with wasting and electrical changes, and few sensory symptoms are present in all. Recurrent attacks following short periods of complete recovery may or may not occur, and neural hypertrophy too, may or may not be present.

I suggest that all these forms of recurrent or progressive polyneuritis, excluding Dejerine's familial type, whether associated with enlargement of the nerves or not, be grouped together as variations included under the description, chronic progressive (endotoxic) polyneuritis.

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VISUAL DISORIENTATION IN HOMONYMOUS HALF-FIELDS.

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DEFECTIVE spatial orientation in the visual fields as a result of bilateral cerebral lesions has been described by a number of observers, notably by Gordon Holmes [1, 2]. By this term is meant inability to localize objects seen in the three planes of space, especially to estimate absolute and relative distance. Sometimes stereoscopic vision is lost, but this has been exceptional [1, 4, 5]. Certain other disorders of function, more or less intimately related to visual disorientation, may be found associated with it, but not all in the same case, such as visual inattention, difficulty in bringing an object into central vision and in maintaining fixation on it when moved, defective pupillary reaction on accommodation, and conjugate convergence of the eyes, reduction of the blinking reflex and visual agnosia.

In the recorded cases of impaired visual orientation the lesions, chiefly from war wounds, have, however, been bilateral in the parietal lobes, so that the visual field as a whole has been involved; and in addition some limitation of the visual field for ordinary test-objects has complicated the clinical picture, although Holmes rightly concluded that this has no bearing on the problem of the interpretation of the nature of the defect. Visual acuity was, as a rule, normal, or nearly so.

The purpose of this preliminary report is to show that spatial disorientation may occur in homonymous half-fields alone, as a result of unilateral lesions of the parietal lobe. For the present, I will briefly describe two cases only in which the defect was unmistakable. In both it was present without any essential impairment of the visual fields or acuity. Neither patient was aware of his visual defect. The following are abstracts of the notes on these cases :—

Case 1.—W. T. W., aged 58, retired from business, was brought by his doctor on May 11, 1933, as a suspected case of cerebral tumour. For six months he had had occasional short attacks of slight giddiness usually when driving his car.

Four weeks ago he fell when climbing a ladder, but had no recollection of what happened until he found himself lying on the ground. There were no immediate bad effects of the accident, but three days later he became unusually tired and sleepy, and had been so since. It was noticed by others that he had difficulty in expressing himself and did not use his right arm as much as before. Since the accident he had had an occasional slight vertex headache, not especially in the morning, and had once vomited after drinking some brandy.

To inquiries, he admitted that his sight had sometimes been misty, but he was unaware of any other visual disturbance. There had been no visual or auditory hallucinations.

On examination, he was cheerful and intelligent, but was rather slow in answering questions, and in carrying out tests, partly due apparently to difficulty in understanding what was required of him. He could not always distinguish between right and left, and when asked to perform the more complicated tests in the examination, he was apt to become confused. Without going further into details there was some dysphasia, but no visual agnosia. There was gross bilateral papilloedema. Visual acuity was $\frac{6}{18}$, partly in his right eye and $\frac{6}{18}$ in his left. Visual fields to confrontation tests were full, but were not charted until after the operation three weeks later, when he was alert and clear mentally. At that time his visual fields were full at all angles to small test-objects except that his left blind spot was considerably enlarged with corresponding depression of the temporal half-field of his left eye in the small isopters.

Localization and estimation of distance were excellent in central vision and in his homonymous left half-fields, whilst in his homonymous right half-fields he invariably made mistakes. In the horizontal plane he often pointed to the right of the test object, but in the vertical plane he was less consistently at fault. His estimation of distance was, however, grossly impaired, and he usually overshot the mark. These defects were found by different observers on several occasions and were perhaps more in the upper than in the lower quadrants. They were greatest in the peripheral parts of the fields and least towards central vision.

There was no visual inattention and stereoscopic vision was unaffected. Pupillary reactions were prompt and sustained and ocular movements were normal except that there was occasionally some difficulty in turning his eyes to the right and in maintaining fixation on an object in that direction. To the left fixation was always good. He found his way about quite easily and did not bump into obstacles. He had no difficulty in finding objects with his hands or in feeding himself.

For the rest, there was slight right hemiparesis, with corresponding reflex changes. Sensibility to light touch and pin-prick, tactile discrimination, vibratory sense and stereognosis were good and equal on the two sides. Tactile localization, however, was faulty in the fingers of his right hand and postural sensibility in his right hallux.

His cardiovascular system was normal for his age.

The resting cerebrospinal fluid pressure was over 300 mm., and the fluid contained 0·075 per cent. of protein but no other abnormality.

Stereoscopic radiograms of the skull were negative.

Exploration was carried out by Mr. Hugh Cairns in two stages because of excessive bleeding. At the second operation on June 5 a purplish-red tumour, spongioblastoma multiforme, was mostly excised from the posterior part of the left parietal lobe. It was about 6 cm. in diameter and reached to within 1 cm. of the medial surface of the hemisphere, and below did not quite reach the temporal lobe. He made a good recovery from the operation.

On August 5, two months after the operation, he was examined for the last time and the same defect in visual disorientation in his homonymous half-fields only was found. He could now turn his eyes and keep them fixed on an object as well to the right as to the left. There were no additional physical signs. His general condition at that time was good and he was an excellent witness.

In November, 1933, five months after the operation, he died, after having been comatose for some weeks.

A post-mortem examination was carried out. Dr. Dorothy Russell reported that there was considerable bulging of the left parietal lobe at the site of operation and the dura was adherent to the brain over part of this area.

The adjacent part of the superior longitudinal sinus was obliterated by growth throughout a length of 7 cm. Coronal sections of the brain revealed a tumour in the left parietal region up to 8·3 cm. from side to side, 5·6 cm. from above downwards and about 8 cm. from before backwards. Microscopically, the tumour extended as far as the upper temporal convolution on the left side. It invaded the falx and dura over the site of operation and extended to the right of the middle line as a nodule (2·3 cm. diameter) in the mesial aspect of the right parietal lobe. The cut surfaces of the tumour showed a central area (3·5 cm.) of necrosis and numerous hæmorrhagic areas up to 1 cm. in diameter. Elsewhere it was composed of white granular tissue and was poorly defined. There was considerable softening of the left hemisphere. The body of the left lateral ventricle was flattened.

Microscopic examination.—The tumour was a spongioblastoma multiforme invading the superior longitudinal sinus and dura. Numerous areas of hæmorrhage and necrosis and organizing thrombosis of many small veins were present.

Comment.—After death the tumour was found to be extensive and to have invaded not only the superior longitudinal sinus and the cortical veins but also the right parietal lobe. This, however, was five months after the operation and three months after the last clinical examination when, as at several previous examinations, the defect in visual orientation was strictly unilateral. The tumour also was a malignant glioma.

Summary of visual defects.—There was visual disorientation in right homonymous half-fields with preservation of stereoscopic vision and visual attention. He was able quickly to fix his gaze on an object and to maintain it to his left, but before operation less consistently to his right. The blinking reflex was not tested. Pupillary reactions and conjugate convergence were normal. Visual acuity was moderately reduced. The sole impairment of the visual field for ordinary test-objects was enlargement of the blind spot in the left eye due probably to secondary optic atrophy. The patient was unaware of his visual disorder.

Case 2.—T. A., aged 34, farmer, was admitted to the London Hospital on July 10, 1934, under Mr. Hugh Cairns.

He had been an exceptionally healthy man until six or seven years ago when he began to get sensations of fullness in his head which were relieved by occasional epistaxis. According to his father, he had, for about the same length of time, become rather sluggish and sleepy.

For the past two years, from which time the patient dated his illness, he had suffered from severe frontal headaches which recurred almost daily and at any time, but worse at night. For a time vomiting, preceded by nausea, accompanied the headaches.

About six months after the onset of the headaches he had his first attack of unconsciousness which lasted for two hours. He had two subsequent attacks, four and six months after the first, but unfortunately none of them had been observed. He recollected a short warning after the second attack only, but could not describe it, but said that he "gripped hold of something." Since the last epileptic attack his headaches had been more severe. On being questioned about his eyesight he admitted that for about six months before the onset of his headaches he had had attacks of dazzling lights in front of his eyes, always whitish-yellow in colour, lasting for five to ten minutes and relieved by shutting his eyes or stooping. Later these crude visual hallucinations tended to accompany the headaches when they were severe. He could not say whether they were confined to one side or not.

On examination he was mentally rather dull and slow. There was slight dysphasia, chiefly for reading, but no visual agnosia. There was severe bilateral papillœdema, right more than left, with flame-shaped hæmorrhages near the discs. Visual acuity was $\frac{6}{18}$ right and left. He had no difficulty in fixing objects and moved his eyes freely. At first there was incomplete right homonymous hemianopia with gross defect of localization of objects and estimation of distance in his right homonymous half-fields. He usually pointed below and beyond the object. In central vision and his left half-fields there was no visual disorientation. There was visual inattention in his right half-fields and he had some difficulty in finding his way back to the ward from the examination room. He could feed himself and accurately grasp near objects with his hands. Later, the right homonymous hemianopia became complete except for sparing of central vision, but there was at least no obvious loss of stereoscopic vision. The pupils and ocular movements were normal in every respect including the pupillary reactions on accommodation and conjugate convergence of his eyes.

On his right side, slight cutaneous anæsthesia and analgesia with impairment of vibratory sense and postural sensibility were found. Voluntary power, tone, co-ordination and reflexes were, however, unaffected.

Stereoscopic radiograms of his skull were negative.

Operation.—On July 17, 1934, Mr. Hugh Cairns explored the left parieto-occipital lobes and found an astrocytoma (proved later by histological examination), presenting on the outer surface of the parietal lobe. Anteriorly, it reached almost to the Rolandic vein and posteriorly to the junction of the parietal and occipital lobes, superiorly to the middle line, and inferiorly (subcortically) to just above the Sylvian fissure. The tumour, which was lobulated and measured over 6 cm. in diameter, was in most places easily separated from the surrounding brain tissue. Anteriorly it had a triangular prolongation extending along a fissure which was either the Sylvian or the one above it.

He recovered well from the operation.

On August 11 his visual fields were full except for small test objects. He no longer had any difficulty in finding his way about. Visual attention was good, although a week before it was still impaired in his right half-fields. Stereoscopic vision was intact. But in his right homonymous half-fields there was still gross spatial disorientation, especially for absolute distance. Estimation of relative distance was less faulty. The defect was confined to the extracentral parts of the fields and became increasingly great towards the periphery and appeared to be greater in the upper than in the lower quadrants. In the outer parts of the fields, he almost invariably pointed internal to the test-object and beyond it. In central vision and his left homonymous half-fields spatial orientation was accurate.

In his affected half-fields he recognized, without hesitation, the shape of a cube, a sphere, a pyramid and a cylinder, when held at from 20 to 30 degrees from fixation point.

Visual fixation, pupillary accommodation and conjugate convergence were all excellent and vibratory sense and postural sensibility had recovered.

On September 21, 1934, two months after operation, he was re-examined. His health was excellent. Visual acuity was $\frac{6}{6}$ right and $\frac{6}{12}$ left, and J.1 both sides. Visual fields were now full to the smallest test-object. But visual disorientation, although less than before, was still present and confined to his right homonymous half-fields.

He lived in Yorkshire and, in consequence, he could not be frequently examined.

We heard that on April 2, 1935, nine months after the operation, he was found dead in a ditch, after having been back at full work for some weeks and in excellent health. His doctor concluded that the cause of death was an apoplectiform seizure, but a post-mortem examination was, unfortunately, not carried out.

Summary of visual defects.—There was visual disorientation in his right homonymous half-fields without loss of stereoscopic vision. Visual inattention in his right homonymous half-fields was at first present but disappeared about a fortnight after excision of the tumour. The patient could rapidly fix his eyes on an object and follow it when moved. The blinking reflex was not tested. The pupillary reactions on accommodation and conjugate convergence were good. Visual acuity was slightly impaired. There was right homonymous hemianopia, at first incomplete and later complete, but two months after excision of the tumour the visual fields were full to small test-objects. Visual disorientation persisted but was less than before The patient was unaware of it.

DISCUSSION.

Since the disturbance of visual orientation was confined to homonymous half-fields the number of tests that could be applied to demonstrate the defect was limited, all the more when central vision, at least in the opposite half-field, was apparently unaffected. Nevertheless, other observers who examined the patients were convinced of its reality. It was clear that these patients, as well as others not recorded in this paper, were unable to localize objects seen but to one side only, and the errors were greatest in regard to distance. As was to be expected, the defect progressively increased from the centre towards the periphery of the visual field. But the patients, themselves, were unaware until the tests were carried out that their vision was affected in this way. They could accurately reach with their hands for food or anything near them and, in a normal way, avoid obstacles in their path. Stereoscopic vision was intact and there was no difficulty in Case II, and, after the operation, in Case I, in fixing with their eyes an object, whether it was stationary or moving. In addition, accommodation and convergence were intact. The preservation of these functions was largely due to retention of central vision, at least in the normal half-fields.

Visual inattention was present in the second case only and disappeared soon after the operation although disorientation persisted. This observation confirms Holmes' opinion that it does not form an essential part of the syndrome of disordered space perception.

In short, the two cases which are recorded in this paper show that: (1) Visual disorientation in homonymous half-fields can result from lesions of the opposite parietal lobe; (2) this defect can be dissociated from other more or less closely related disorders of visual function which also have been found to follow lesions of roughly the same part of the brain; and (3) visual disorientation may be present without limitation of the visual fields for ordinary stimuli or serious disturbance of central vision. Thus, the patient may be unaware of his deficiency for, under these circumstances, it does not give rise to obvious disability. As a corollary, to be discovered, it has to be searched for by the observer.

In regard to the situation of the lesion, the tumour in both cases extensively invaded the parietal lobe including the supramarginal and angular gyri. The ascending parietal convolution was little affected directly by the tumour, and the optic radiations had escaped. For the purpose of localization, that is as far as it is reasonable to go for the use of tumour material in this respect is notoriously limited. Holmes from his cases of bilateral war wounds and from other recorded cases, also bilateral, concluded that visual disorientation resulted from lesions in the region of the supramarginal and angular gyri. The ideal pathological case would be one of circumscribed cerebral softening.

As to the nature of the disturbance of function, I have nothing to add to the views already expressed by Holmes. Visual localization in the coronal plane largely depends on local sign of the retinal elements. Estimation of absolute and relative distance is, however, a much more complex function and is the result of the integration of immediate sensations and impressions from the retina, ocular muscles, labyrinth, neck and body with accumulated past experience. In other words, it is a function that is acquired by learning.

Visual disorientation may occur when the association pathways from the calcarine visual cortex to other parts of the brain are interrupted and, so far as is at present known, the nodal point appears to be in the region of the supramarginal and angular gyri in the parietal lobe.

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CERTAIN ANATOMICAL AND PHYSIOLOGICAL ASPECTS OF THE MENINGES AND CEREBROSPINAL FLUID.[1]

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THE cerebrospinal fluid is a clear, limpid liquid of slight viscosity and low specific gravity, which fills the cerebral ventricles and surrounds the entire neural axis. Approximately one-tenth of the intradural volume is represented by this fluid in mammals; the usual amount occurring in man is therefore between 100 and 150 c.c. Normally of a negligible protein-content, almost cell-free, the fluid contains the same crystalloids as does the blood, with sodium salts predominating; its average pH value is given as 7·35. These chemical and physical characters of the fluid caused Halliburton [27] to term it "an ideal physiological saline solution."

Writers in the Hippocratic corpus must have had some knowledge of the cerebrospinal fluid, for hydrocephalus was recognized as a distinct pathological entity. In his discussions of animal spirits, Galen similarly recorded the existence of large quantities of water on the brain: this influence of Galenic thought extended uninterruptedly for over a thousand years. It was not until the eighteenth century that adequate descriptions were given of fluid in the subarachnoid space as well as in cerebral ventricles—Cotugno [9] and Haller [26] both should be named for their contributions to the subject. Yet our modern conceptions must be related to the comprehensive description of this perimedullary fluid, given by Magendie [41, 42] slightly over one hundred years ago.

During this century since Magendie's publications, information regarding the fluid and its pathway has slowly accumulated. We now have detailed knowledge regarding the mammalian meninges as fluid-containers; Kappers' [36] studies in other vertebrate classes have added much, but the data are by no means as complete. For the most part the story of cerebrospinal fluid must therefore be restricted to mammals —to man and particularly to the common laboratory animals. It is perhaps unfortunate that the subject must be discussed to-day, as in many of the most important problems of the fluid general agreement or acceptance of a viewpoint has not yet been reached: unanimity of opinion may exist only among the workers of a single school. In consequence, it behoves investigators in this field to speak circumspectly, to consider but few of the concepts as final: we must weigh evidence and qualify our conclusions. Many essential problems of the fluid are to-day hardly at a stage for even a temporary deduction, even a hesitant hypothesis; yet all in all during the past few decades there has been advance in knowledge, and it is with certain restricted aspects of this advance that this essay will deal.

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The difficulty of divorcing structure from function holds particularly true for the embryology of the meningeal spaces through which the cerebrospinal fluid circulates. The early investigations by His [34, 35] and Kölliker [38] seemed to establish the mesodermal origin of the three mammalian meninges; this concept was supported by Salvi's [46] morphological findings as well as by Sterzi's [48, 49] comparative investigations. My own histological studies [54], based on extensive series of pig and human embryos, led me to unqualified acceptance of this general thesis of development of the three membranes from the middle germ layer. But this idea of a purely mesodermal origin of the meninges, apparently confirmed by Van Gelderen's [25] studies on the fish and by Clermont's [8] on the mole, has in recent years been questioned by Harvey and Burr [28]. Such an attack on the specific origin of any tissue, particularly around the head-end of the nervous system, seemed inevitable in view of the work of the experimental embryologists of the last thirty years, for a mixture of ectodermal and mesodermal elements has been shown to occur in many amphibian forms. Noting a difference in reaction to injury of the dura and of the pia-arachnoid, Harvey and Burr transplanted, in Amblystoma larvæ, portions of the central nervous system, with and without neural crest cells. After growing in the host, it was found that the only transplants to develop a leptomeningeal space were those which had neural crest cells—in other words, the leptomeninges needed an ectodermal contribution.

These deductions of Harvey and Burr were promptly objected to by Louis Flexner [15], who performed similar experiments on the same amphibian form. This investigator found a meningeal space to develop only about those transplants which extruded fluid into the tissues of the host—the passage of fluid through the embryonic tissue about the transplant seemed to cause the formation of definitive channels remarkably similar to those of the normal subarachnoid space. This fluid-passage rather than the inclusion of neural crest cells was considered by Flexner to be the determining factor. Even more recently Harvey, Burr, and Van Campenhout [29] have presented additional evidence; they accept certain aspects of Flexner's work, but re-emphasize the blending of mesodermal and neural crest elements. The problem is still in the stage where final agreement does not exist for all vertebrate classes, though the stages of differentiation of a mesoderm, or mesectoderm, into three meninges, are fairly well understood for mammals.

My own studies [54] on this differentiation of the perimedullary mesenchyme were made on living pig embryos in which the cerebrospinal fluid was replaced by an isotonic foreign solution (potassium ferrocyanide and iron ammonium citrate). This foreign solution, distributed by the normal processes of the organism and then precipitated in situ, gave histological evidence of the initiation of the spread of the fluid from the ventricles in 14 mm. embryos and of the filling of a complete subarachnoid space at 26 mm. In the stage of first extraventricular spread of the fluid (14 mm.) the choroid plexuses, both in pig and human embryos, are just beginning to tuft. This coincidence of development of plexus and extraventricular expulsion of fluid, as well as histological findings, led me to assume that the circulation of fluid through the perimedullary mesh was a causative factor in the differentiation of the subarachnoid space. This general idea of a functional differentiation of the perimedullary mesenchyme was accepted ten years later by Flexner in his transplantation experiments and was considered a factor by Harvey and Burr.

The close relationship between the development of choroid plexuses and extraventricular spread of cerebrospinal fluid emphasizes again the evidence for the intraventricular origin of the fluid. That by far the greater portion of the fluid arises in the cerebral ventricles has long been known from study of cases of internal hydrocephalus. Even to-day, when we have at hand histological, embryological, pathological, pharmacological and experimental evidence supporting the thesis that the choroid plexuses are the chief elaborators of the fluid, there are in the minds of some workers doubts as to the validity of the hypothesis. Thus the occurrence of inclusions within the cells of the choroid plexuses [30, 31, 32] has been recently interpreted as supporting the concept that these vascular tufts with their cylindrical epithelium are organs for the absorption rather than the production of cerebrospinal fluid.

But the great mass of data upon which is based the idea of an elaboration of cerebrospinal fluid by the choroid plexuses cannot be interpreted in any other way as satisfactorily. Certainly to-day there is no reason to discard this concept in favour of any other.

If one accept the hypothesis that the choroid plexuses elaborate by far the major portion of the fluid, the problem of the mechanism of its production immediately presents itself. Since the earliest histological descriptions by Faivre [14] and Luschka [40] of the glandular type of epithelium covering the plexuses, repeated controversies have raged as to whether the fluid is a true secretion or a filtrate. Until recently not many data of permanent significance were advanced, but the last few years have witnessed many attempts by chemists and physiologists to reach a conclusion in this important question. The essence of the problem is the determination of the rôle played by the membranes separating the blood and the cerebrospinal fluid in the distribution of ionic and molecular species between the two fluids. The problem particularly concerns itself with the question whether the cells of the plexus, the walls of its capillaries, and the connective tissue of the stroma of the plexus perform work in the production of cerebrospinal fluid, or whether substances are distributed between blood and cerebrospinal fluid as would occur across an inert lifeless membrane. A large group of investigators, notably Fremont-Smith and his associates [20, 21, 22, 23, 24], has concluded that the distribution of all diffusible ions between the two fluids is in agreement with the predictions of Donnan's law; cerebrospinal fluid therefore becomes a dialysate or filtration-product from the blood. Analyzing the chemical data of the blood and fluid from a thermodynamic standpoint, Louis Flexner [16] has shown that approximately thirteen calories of energy are required for the formation of a litre of cerebrospinal fluid; a free energy change of only 0·9 calories is to be explained by capillary pressure. Ultrafiltration, i.e. dialysis plus hydrostatic pressure, Flexner judged to be an inadequate explanation of the elaboration of the fluid. He concluded on the basis of present evidence that the fluid is to be considered a secretion, using that term to mean that the cells do work in its production. Flexner's analysis of the problem is of utmost significance in the present state of our knowledge of the cerebrospinal fluid.

Accepting then this conclusion that the cerebrospinal fluid is secreted by the choroid plexuses (with possibly a small addition from the ependymal cells themselves) it becomes necessary to trace the fluid in its further course. Poured into these neural cavities in small amount

(12 c.c. per day in a cat according to Flexner and Winters [19]) the fluid travels caudalwards to the fourth ventricle and thence passes, either by foramina or permeable membranes, into the subarachnoid space. The fluid flows rapidly into the basilar cisterns, more slowly upwards over the cerebral hemispheres; it moves very tardily downward about the spinal cord. Everywhere in this passage it is retained within membranes covered with flattened mesothelial cells, which as Essick [13], Woollard [67], Kubie and Schultz [39] have shown, exhibit functional changes in morphology. Within the subarachnoid space a small addition to the cerebrospinal fluid probably is derived from the perivascular channels, though Schaltenbrand and Bailey [47] consider this source of fluid as not demonstrated.

In the cerebral subarachnoid space the cerebrospinal fluid comes into intimate contact with the dural venous sinuses. All of the work of the last fifty years indicates that the major process of absorption is a direct and rapid one into the venous system, and that there is also a minor process of relative slowness into the lymphatics. Accepting this generalization, there are still differences of opinion as to the exact mode of return of the fluid to the venous system. Twenty years ago I came to the conclusion [51, 52, 53] that the pathway of absorption was through the arachnoid villi—the microscopic normal precursors of Pacchionian granulations which have recently been so thoroughly studied by LeGros Clark [7] and by Winkelman and Fay [66]. The villi are essentially invaginations of the arachnoid tissues through the fibrous walls of dural sinus so that leptomeningeal mesothelium comes to lie directly beneath vascular endothelium. This hypothesis of fluid-drainage which was based on histological observations made after subarachnoid injection of an isotonic solution of foreign salts in living animals and subsequent precipitation of the salts in situ, still seems to me the most acceptable of the theories of escape of fluid. Elman's [12] description of spinal arachnoid villi, projecting into the segmental veins, has widened the hypothesis to account for spinal drainage. The general idea of passage of fluid through these specialized structures has been questioned by Dandy [10] who freed the brain from its connection with the sagittal, circular and transverse sinuses, leaving the pia-arachnoid supposedly intact. Since no subsequent discomfort was apparent in the dogs, Dandy concluded that the villi play no role in absorption—a conclusion which takes no account of spinal villi, of the possibility of regeneration or re-establishment of channels, and of the fact that an increased pressure of the cerebrospinal fluid may lead to the same rate of absorption even with smaller absorptive surfaces. But while we cannot regard as established any other theory of drainage of cerebrospinal fluid, we must realize fully the limitations of any method of demonstration of a fluid-pathway which depends upon the introduction of foreign salts for the purpose of outlining a route of absorption. Both ante mortem and post mortem diffusion of the crystalloids has always to be considered: it is now particularly desirable that some new method of investigation of this problem be devised.

When beginning work upon cerebrospinal fluid, I gave but minor consideration to the physical forces involved in the absorption of the fluid into the venous system. At that time [52] the mechanism seemed to be one of filtration through the arachnoid mesh and mesodermal membrane from a point of higher to a point of lower hydrostatic pressure. Since that time I have desired to return to this all-important problem, particularly in view of the fact that our knowledge of osmotic and hydrostatic pressures has advanced greatly within this period. But it was impossible to attack experimentally these questions without a method for recording small amounts of fluid-absorption. Two years ago Mortensen and I [44] devised a simple pipette-reservoir system which permitted measurement of the absorption of small quantities of foreign solutions from the subarachnoid space of living animals under maintained pressures. With this apparatus set at normal pressure of the cerebrospinal fluid, periods of small intake of Locke's solution were followed by similar periods of outflow of fluid; at the end of an hour or so no absorption of the isotonic solution from the external system could be observed, even though the cerebrospinal fluid was being produced at a normal rate. When, however, the pressure in the external system was raised (thus raising the pressure throughout the whole subarachnoid space) definite absorption was recorded each minute. We were able to confirm the long-established observations that the higher the pressure of introduction of an isotonic solution the more rapid was its absorption from the subarachnoid space. We used relatively high pressures, multiples of the existing cerebrospinal fluid pressure, and found that a linear relationship existed only in the low pressure-range (up to three or four times normal pressure); above this point a marked increase in the rate of introduction of the isotonic fluid occurred.

During the last year, these experiments on etherized dogs have been continued, using various kinds of foreign solutions—crystalloids, proteins, &c.—for determination of the physical forces concerned in absorption of the fluid. With measurement of the intracranial venous pressure in the sagittal sinus, the rate of absorption of Locke's solution was ascertained for various pressures above the normal. Since the crystalloids of the cerebrospinal fluid, of the Locke's solution and of the blood are approximately the same qualitatively and quantitatively, the only effective pressures causing absorption of the Locke's solution were assumed to be the hydrostatic pressure (subarachnoid pressure minus sagittal venous pressure) and the osmotic pressure of the colloids of the blood. As the osmotic pressure of the colloids of the blood could be taken to be constant during the period of observation, it was possible to plot the rate of absorption in c.c. per minute against the total effective pressure—hydrostatic pressure plus colloid osmotic pressure of blood. Such a plot showed a clear-cut linear relationship, and suggested that the assumed effective pressures were those responsible.

Under identical experimental conditions in the living dog, the rates of absorption of Locke's solution were next compared with solutions of various protein-content. Heterologous dog serum and solutions of gelatin and casein all showed rates of absorption considerably slower than that of Locke's solution. At the end of the observation samples of blood-serum, of the foreign protein-solution, and of the cerebrospinal fluid (as withdrawn after the introduction of the foreign protein) were set up in celloidin thimbles for determination of colloidal osmotic pressures. The hydrostatic pressure was easily calculated by subtracting the intracranial venous pressure from the established subarachnoïd pressure ; the osmotic pressures of the colloids of the two fluids were related to the computation by using the difference between the osmotic pressures of the blood and the protein-containing cerebrospinal fluid in the case of the protein-solution, and by using the colloid osmotic pressure of the blood alone in the case of the Locke's solution. Calculating the total effective pressure (hydrostatic plus colloid-osmotic) and plotting against the rates of absorption of the two solutions, a straight-line relationship was again found. This linear relationship seems to indicate that the physical forces underlying the normal process of absorption of cerebrospinal fluid are all to be accounted for in this determination of total effective pressure—the hydrostatic pressure-difference between subarachnoid space and cerebral venous system plus the colloid osmotic pressure of the blood.

With this demonstration of the effective pressure regulating the absorption of the cerebrospinal fluid, the next step was to ascertain the rates of absorption of non-protein solutions whose concentration of crystalloids differed markedly from those of the blood. Distilled water was first used : to our surprise its rate of absorption did not vary from that of Locke's solution. When plotted against effective pressures (disregarding its theoretical lack of crystalloid content), the distilled water and the Locke's solution formed the same straight line. A similar result was obtained with twice-normal Locke's solution where the salts were added to the solution in double concentration. The most plausible explanation for this extraordinary phenomenon is that within the subarachnoid space the interchange of water and ions was so rapid that the foreign solutions were quickly rendered isotonic.

With this rapid restoration of simple solutions to isotonicity within the subarachnoid space, an attempt was made to ascertain if the same phenomenon would hold for crystalloids of far larger molecular size. Following the important observations of Bullock, Gregersen and Kinney [5], upon the slow conveyance of sucrose across membranes, a 5 per cent. solution of this sugar in Locke's solution was introduced into the subarachnoid space. The rate of absorption of this solution was found to be much slower than that of Locke's solution: when plotted against total effective pressure its rates of absorption formed a straight-line relationship, but at a far lower level than with the Locke's solution. Here the large molecule of sugar apparently exercised an osmotic pull against the colloid osmotic pressure of the blood, decreasing the effective pressure over the short period of the experiment (thirty minutes). This particular phase of the research is only just under way and far more work is required before any broad generalizations can be attempted.

With these data on the subarachnoid absorption of non-protein and protein-containing solutions at hand, it now becomes possible to speak with some exactness of the physical forces having to do with the normal absorption of the cerebrospinal fluid in four-footed mammals in which the central nervous system is so largely held in a horizontal position with only the head at a different level. The total effective force which determines absorption is apparently compounded normally of the hydrostatic pressure (subarachnoid pressure minus cerebral venous pressure) and of the colloid osmotic pressure of the blood. In the four-footed mammal the hydrostatic element is of relatively small moment as the pressure of the cerebrospinal fluid customarily exceeds the sagittal venous pressure by only 15 to 35 mm. saline, and occasionally the former is less than the latter. The major effective force, therefore, becomes the osmotic pressure of the colloids of the blood, for the cerebrospinal fluid is almost totally lacking in proteins. This osmotic pull of the blood colloids lies in the neighbourhood of 250 and 300 mm.

saline. This force seems sufficient to insure the constant absorption of cerebrospinal fluid at the same rate at which it is produced. But the question immediately arises as to whether alterations in the general posture of the mammal will affect this mechanism of absorption.

This question cannot yet be answered in its entirety, but it has importance not only in regard to the physiology of the four-footed mammal, but also in regard to the assumption of erect posture by man, in whom we are, of course, primarily interested. In its basic form, the change in posture can have effect in the absorption of cerebrospinal fluid only if the positional changes in its pressure are such as radically to change the magnitude of the hydrostatic pressures which are effective in causing the passage of the fluid back into the blood-stream, it being assumed that the colloid osmotic pressure of the blood would remain constant during such a positional change. The problem, then, is one of information regarding the changes in pressure of the cerebrospinal fluid on alteration of position from the horizontal to the two vertical positions, and is intimately connected with the protection of the central nervous system against atmospheric pressure.

It should be a source of great pride to all British anatomists that Alexander Monro [43], the second, should have promulgated a doctrine of basic importance to intracranial physiology. In 1783 this Scotch anatomist ventured the hypothesis that the quantity of blood circulating within the cranium must at all times be constant, "as the substance of the brain, like that of the other solids of our body, is nearly incompressible" and as the brain "is enclosed in a case of bone." Having no knowledge of the cerebrospinal fluid, in spite of the publications of Haller and Cotugno some years before, Monro assumed a constant intracranial volume in which alterations in arterial volume must be compensated for by reciprocal changes in the venous volume. The original hypothesis, receiving apparent verification in the observations of George Kellie [37], has become quite properly known as the Monro-Kellie doctrine. Modified by Burrows [6], who, in 1846, introduced the cerebrospinal fluid into the concept, the doctrine has come down through a century and a half without great change in its essentials: the entire physiology of the intracranial fluids has to be discussed in terms of the limitations imposed by the "closed box" character of the bony containers—skull and vertebral column.

During the last forty years great interest in the doctrine has been apparent. Leonard Hill [33], in his important study of intracranial hydrodynamics, considered the hypothesis essentially sound; Dixon and

Halliburton [11] tended to regard it as not affecting in any major way the pressure-relationships within the cranium. My own interest in the doctrine came through experiments with McKibben [64, 65] and with Hughson [61, 62, 63] in which marked alterations in the pressure of the cerebrospinal fluid were obtained by the intravenous injection of solutions whose salt-content varied markedly from that of the blood. With the introduction of large amounts of strongly hypertonic solutions (30 per cent. NaCl) into the blood-stream, negative pressures (i.e. below atmospheric) were frequently observed within the cerebrospinal fluid. Such negative pressures could exist only if the bony containers of the nervous system functioned as a closed box, so that atmospheric pressure could not directly affect the tissues and fluids within the container. It was realized then that this demonstration of the rigid box character of the skull and vertebral column was achieved by drastic means and gave no information regarding the smaller elements of elasticity within the system. Subsequent investigation has given more detailed knowledge of the limitations of the doctrine which may still be considered to be essentially sound.

Six or seven years ago, experiments dealing with the pressure-changes about the central nervous system on abrupt tilting of an animal from the horizontal to the two vertical positions were undertaken. In the first of these observations [55] it was learned that in dogs with a spinal length of approximately 400 mm. the pressure-changes in the cerebrospinal fluid on tilting were only one-third to one-fourth of the length of the hydrostatic column of the fluid. The fact that the whole hydrostatic column of cerebrospinal fluid is not effective in the vertical positions of the four-footed mammal indicates [58] that the bony coverings of the central nervous system do protect this structure from atmospheric pressure and thus function like a closed box. If this protection were perfect no measurable pressure-changes in the cerebrospinal fluid on tilting would occur. The occurrence, however, of these measurable pressure-changes leads to the idea that there are within these bony coverings elements of elasticity which allow a certain dislocation of fluid to occur on positional change. Such pressure-changes can be measured in an external system which permits no external dislocation of fluid: the dislocation of cerebrospinal fluid therefore occurs within the dural sac whenever positional change of the mammal is effected.

This dislocation of the fluid on tilting from the horizontal to the vertical positions has led to the determination of the coefficient of elasticity of the system [17, 18, 59, 60]. By the use of manometers of different bores, pressure-changes and volume-changes in the fluid on tilting were obtained, for as the caliber of the manometer was increased the pressure-change became less and the volume-change greater (until the limit of fluid-dislocation was reached). The elasticity of the system was then determined in exact terms by substituting in the standard physical formula where the elasticity is considered to be the stress divided by the strain—i.e. $E = dP / \frac{dV}{V}$. Using this formula, as had been done in a somewhat different way by Ayala [1, 2], it was found that the elasticity of the intradural contents was of approximately the same magnitude in the four mammals tested—dog, cat, macaque and chimpanzee; the elasticity showed definite differences in the age-groups of these laboratory animals. The coefficient of elasticity was of the same magnitude when determined from the pressure-changes and volume-changes on head-down and tail-down tiltings. From this identity of the elastic components it seemed fair to conclude that in the assumption of the erect posture by certain mammals no special mechanism of adjustment for the hydrostatic column of cerebrospinal fluid had been developed [56, 57].

With such elasticities existing within the cranium and vertebral column, permitting a dislocation of fluid from the uppermost to the lowermost portions of the nervous system in the vertical position of the mammal, it becomes interesting to speculate as to the anatomical and physiological elements which give rise to this elasticity. First of all, it is apparent that the vascular bed—particularly the great venous bed—contributes an essentially large element of elasticity, for changes in the volume of the cerebrospinal fluid are rapidly compensated for by reciprocal change in the venous volume. Likewise there is an element of elasticity in the epidural space of the spinal region: the spinal dura, fairly rigid against expansion outward, can collapse inwardly due to stretch of the epidural trabeculæ and dilatation of the thin-walled epidural veins. And perhaps there is a factor of elasticity in the occipito-atlantoid ligament and in the various intervertebral structures.

Now that we have some conception of the elastic elements about the nervous system it is possible to reach certain general ideas regarding the process of absorption of cerebrospinal fluid in the erect posture. In the four-footed mammal the cranium has been demonstrated to be the chief site of fluid-escape; in a dog of 400 mm. spinal length, tilting to a vertical, tail-down position (erect posture in man) causes a fall in occipital cerebrospinal fluid pressure of slightly over 70 mm. saline while the sagittal venous pressure drops by 80 mm. Such decreases in pressure would result in an intracranial pressure of plus 50 mm. for the cerebrospinal fluid and of plus 30 mm. for the sagittal sinus. Under these circumstances—the figures set down are approximations—absorption of cerebrospinal fluid would still proceed from the cranial membranes as a hydrostatic element (though small) would still be present, and the colloid osmotic pressure would be the same as in the horizontal position. Under these circumstances also, there might possibly be an increased absorption through spinal mechanisms though the rise in systemic venous pressure in the lower part of the animal's body might overcome any increase in the hydrostatic element.

Can this process of reasoning now be applied to the conditions in erect man? The many important observations (particularly by Zylberlast-Zand [68], Pfaundler [45], Ayer [3], and Barré and Schrapf [4], on differences in lumbar pressure of the cerebrospinal fluid in man in the prone and erect position indicate that a comparable dislocation of fluid occurs in man as in the four-footed mammal on positional change. Ayer's finding of a small negative pressure on cistern puncture in man in the sitting position and Walter's [50] stimulating deduction that in erect man the point of atmospheric pressure is in the mid-thoracic region, allow one to hypothesize that in this position man has a negative pressure of not less than minus 400 mm. saline at the calvarium. If, under such circumstances the pressure in man's sagittal sinus be still positive (and on this score we have no information), the hydrostatic element (subarachnoid pressure minus sagittal pressure) would be negative by 350 to 400 mm. This negative pressure would be sufficient to overcome the osmotic pressure of the colloids of the blood and no absorption of cerebrospinal fluid could take place in the sagittal sinus. In the more dependent parts of the nervous system absorption could still proceed. But this is speculation and rests too largely on supposition of pressures rather than upon actual determinations.

These then are a few of the problems, a few of the aspects, of the cerebrospinal fluid which have interested workers during the last few decades. The tale related is woefully incomplete, but the limitations of time prohibit the presentation of an entire viewpoint. More information is needed at almost every corner in these considerations of the fluid ; research alone can supply this needed information but it must go forward with due appreciation both of morphology and of function. That this research will be done there can be no doubt, for this clear, limpid fluid about the nervous system has interested many in the past and it will continue to do so in the future.

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TRAUMATIC LESIONS OF THE OPTIC CHIASMA

BY H. M. TRAQUAIR, NORMAN M. DOTT, AND W. RITCHIE RUSSELL.

DAMAGE to the optic chiasma, as evidenced by the occurrence of temporal defects in both visual fields, is an uncommon complication of head injury. Cantonnet and Coutela [4] in 1906 collected eight cases, and Bollack [3] in 1920 analysed seventeen cases. We have collected records of twenty-seven, and add three further cases which we have recently had the opportunity of studying.

The original records of some of the cases which have been described as injuries of the chiasma appear to be too indefinite to justify inclusion in the series. They are the cases described by Granger [12], by Griffith [13], by Morlan [25], Nieden's second case [26] Coppez second and third case [5] and the cases described by Dejean and Bonnahon [7]. The reason for omitting these cases is, either that the connection between the injury and the visual defect is uncertain, or else that the visual defects described could have been readily produced by lesions of other parts of the visual pathway without chiasmal involvement. A difficulty arises with regard to those cases in which there is complete blindness in one eye and temporal hemianopia in the other. This may be produced by damage to the optic nerve and optic tract of the same side. It may also follow bilateral damage to the optic nerve, as temporal hemianopia may occasionally be produced in this way [33]. As it seems, however, to be more probable that the damage in these cases is to the optic chiasma and to one optic nerve, they are included in this study.

The main features of the published cases are recorded in Table I. We have been unable to obtain the original descriptions of the cases described by Lambert [21], Dumont [9] and Hoffman [15] (Cases 4, 9 and 13). These are, however, mentioned briefly in a table in Bollack's paper, and the particulars given there are included in Table I.

The following are the three cases we have had the opportunity of studying:—

Case 28. Personal case A. A blacksmith, aged 24 years, was admitted to hospital in a semi-comatose condition on December 23, 1933. Shortly before admission he had fallen from a roof on to a concrete pavement, a distance of about 20 ft. We are indebted to Mr. J. W. Struthers for permission to study this case. On admission there was bleeding from the nose, but none from the ears. There was a depressed fracture of the right frontal bone which involved the inner part of the right supra-orbital ridge. X-ray examination showed a large V-shaped fracture of the right frontal region, but there was no visible evidence of the fracture spreading to the base of the skull.

The patient remained in a state of restless stupor for the following week. There was then a sudden rise of temperature, and the cerebrospinal fluid was found to be turbid, though there were no organisms present. After a further period of a week, the temperature returned to normal, and gradual recovery of consciousness occurred about four weeks after the accident.

When examined on January 9, 1934, the line of the fracture was easily felt above the right eye, and there was subconjunctival hæmorrhage on the outer aspect of this eye. Headache was severe and the patient was still stuporose. The pupils were each 5 mm. in diameter and reacted sluggishly to light. There was slight drooping of the right eyelid and limitation of the upward movement of this eye. Ocular movements were otherwise normal.

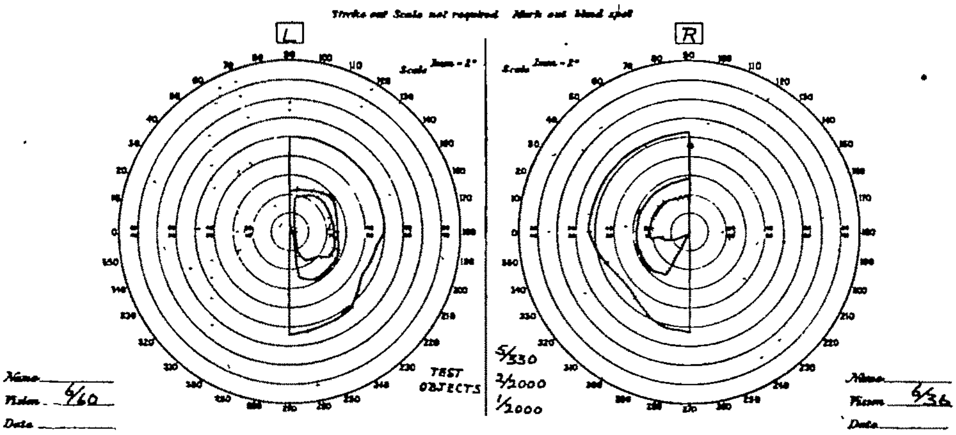

FIG. 1.—Visual fields of Case 28, personal case A.

On January 21, 1934, full consciousness had returned. The sense of smell was impaired on the right side. With each eye the patient was able to read large print with difficulty. The appearance of the optic discs was normal. There was complete bitemporal hemianopia to rough tests. The palpebral aperture was smaller on the right side than on the left. The pupils were very large, 9 mm. in diameter, but equal. They reacted briskly to a spot of light thrown on the temporal half of each retina, but showed no reaction when light was thrown on the inner half of each retina. Ocular movements appeared to be full in all directions, but diplopia was present in whatever direction the eyes were turned. This diplopia remained a crossed diplopia in whatever direction the eyes were looking. Both images were vertical, but the image

TABLE I.—THE MAIN FEATURES OF THE PUBLISHED CASES.

No.	Year of publication	Author	Age	Site of injury	Type of injury	Visual acuity N = Normal		Point of fixation Inter = Intersected Sp. = Spared		Hemianopic reaction	Other cranial nerves affected	Diabetes insipidus	Adiposity	Progress re V.A. Detd. = Deteriorated Imp. = Improved		Period under observation	Other points of interest
						L.	R.	L.	R.					L.	R.		
1	1883	Nieden [26]	28	?	Mining	0	6/6		Inter.	•	R. 6th and 8th	+		I.S.Q.		6 months	Polyuria disappeared in 6 months.
2	1884	Schoeler Uthoff [31]	16	Bi-temporal	Crush	5/40	5/15	Inter.	Inter.								
3	1884	Tuffier [34]	17	R. frontal	Fall	N	N	Sp.	Sp.		R. 1st, 6th and 8th	+					
4	1886	Dumont [9]		Frontal		1/6	0				7th						
5	1894	Peretti [28]	49	R. frontal	Blow	4/36	4/18	Sp. 3°	Sp. 3°	+	1st, R. 6th and 8th	+		Deteriorated (L. blind)		10 months	Crossed diplopia.
6	1899	Karnitzky [17]		Frontal		? N	0										Fracture of L. supra-orbital margin.
7	1902	Kipp [18]	50	R. frontal	Fall	0	5/10		Inter.	+							
8	1904	Lange [22]	20	R. frontal	Fall	6/10	6/6	Sp. 5°	Sp. 5°	+	R. 1st, L. 8th	+					Polyuria for a few weeks only.
9	1904	Hoffman [15]		Frontal		5/6	0	Inter.									
10	1905	Redslob [29]	14	L. frontal	Thrown against ground	0·9	0·1	Sp. 3°	Sp. 3°	?	R. 8th	+		Improved		5 months	Depressed L. frontal fracture
11	1906	Wilbrand Saenger [35]	37	L. frontal	Fall	6/12	6/18	Sp. 4°	Sp. 4°	+				Improved		Few weeks	Depressed L. frontal fracture.
12	1908	Dufour Gonin [8]	11	L. frontal	Fall	Very poor	Very poor	Sp. 40°	Sp. 4°	?				Detd., R. and L.		11 years	
13	1908	Lambert [21]				2/10	1/2	Inter.	Inter.	?	1st, 6th, 8th	+					

14	1912	Sulzer Chappé [32]	20	Frontal	Fall	Good	Good	Sp. 4°	Sp. 8°	+						Depressed frontal fracture.
15	1912	Jess [16]	21	Frontal	Struck a tree	0·5	1·0	Sp. 6°	Sp. 6°	+	L. 3rd	+		Improved	13 weeks	X-ray: frontal fracture extending to sella. Aseptic meningitis.
16	1912	Liebrecht [24]		L. frontal	Fall	5/60	6/18	Inter.	Inter.		R. 6th			L. detd., R. imp.	2 years	Post-mortem.
17	1912	Liebrecht [24]		L. frontal	Fall	0	6/12		Sp. 2°	+					4 weeks	
18	1912	Liebrecht [24]		L. parietal	Fall of brick	Very poor	Very poor	None	None					Improved	Few weeks	
19	1915	Uthoff [11]			Crush			Inter.	Inter.							
20	1915	Uthoff [11]						Inter.	Inter.					Improved		
21	1917	Behr [1]	22	L. temporal?	War wound	6/25	6/18	Sp.	Sp.		L. 3rd	—	+	Improved	18 months	Complete recovery of fields.
22	1920	Bollack [3]	36	R. parietal	War wound	1/100	7/10	None	Sp. 3°	Negve.	R. 6th, L 3rd	—	—	Improved	3 months	
23	1926	Favory [10]	19	R. parietal	Fall	5/6	Very poor	Sp. 3°	None		R. 3rd					
24	1926	Favory [10]	24	R. frontal	Motor car	1·0	9/10	Sp. 50°	Sp. 3°		R. 3rd			Improved	2½ years	Depressed frontal fracture extending to R. anterior clinoid.
25	1926	Okinczyc Renard [27]	24	R. fronto-parietal	Motor car	4/10	9/10	Sp.	Sp.	Negve	R. 3rd	—	—	Improved	6 months	X-ray: R. Fronto-parietal fracture extending to base.
26	1929	Coppez [5]	21	R. frontal	Motor cycle	N	N	Sp. 10°	Sp. 12°							X-ray: Depressed R. frontal fracture.
27	1930	Coutela 6]	30	Frontal	Fall	5/10	5/10	Sp. 5°	Sp. 5°	Negve						
28	1934	Personal Case A	24	Frontal	Fall	6/60	6/36	Inter.	Inter.	+	R. 3rd	—	—	Slight improvement	6 months	X-ray: Depressed R. frontal fracture. Crossed diplopia.
29	1934	Personal Case B	27	Frontal	Motor cycle	0	6/6		Sp. 3°	+	L. 6th	—		Improved	18 months	X-ray: no fracture seen.
30	1934	Personal Case C	40	Frontal	Motor car	6/6	6/36	Inter.	Inter.		1st	—	+			

on the right was slightly lower than that on the left. Apart from a slight degree of deafness of the right ear, there was no further abnormality detected on full examination.

On February 25, 1934, the visual acuity was right (with −1·0): $\frac{6}{36}$, and left (with −1·5): $\frac{6}{60}$. Both optic discs showed marked pallor. The visual fields (fig. 1) showed sharp bitemporal hemianopia with intersection of the point of fixation on both sides. The smallest object elicited a slight defect in the lower nasal field of the right eye. Crossed horizontal diplopia was still present in whatever direction the eyes were turned, and if the patient was instructed to look intently at an object, a slight divergent strabismus became apparent.

Case 29.—Personal case B. A miner, aged 27, was thrown from his motor cycle on June 4, 1932, and was at once rendered unconscious. He was admitted to Mr. J. M. Graham's ward in Edinburgh Royal Infirmary, and we are indebted to Mr. Graham for permission to study the case. The accident caused gross effusion into the eyelids and bruising of the left frontal region. There was bleeding from the nose, but none from the ears. X-ray examination of the skull showed no evidence of fracture. There was a fracture of the left femur and left arm. The patient recovered full consciousness two weeks after the accident. Examination then revealed complete blindness of the left eye, and temporal hemianopia of the right visual field. The pupils were equal, but 7 mm. in diameter. There was complete paralysis of the outward movement of the left eye. Wernicke's hemianopic pupillary reaction was clearly present when tested on the right eye. There was no direct light reaction of the left pupil. Full examination showed no further abnormality. The patient returned to full work underground in January, 1933, by which time the 6th nerve paralysis had completely recovered. There were no post-concussional symptoms.

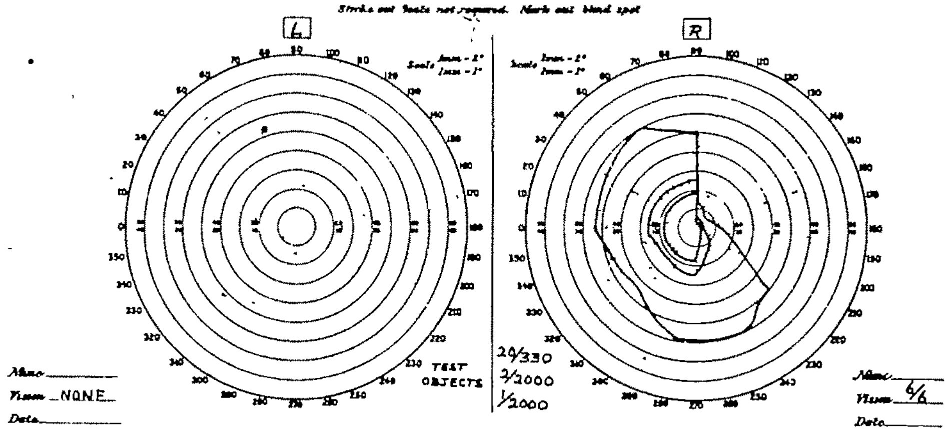

FIG. 2.—Visual field of Case 29, personal case B.

The visual acuity two months after the accident was $\frac{6}{6}$ in the right eye and this was unchanged in March, 1934. The left eye remained quite blind.

The visual field was charted in August, 1932, and in March, 1934, with a similar result (fig. 2). The hemianopic nature of the field defect is brought out by the graded perimetric chart. Wernicke's hemianopic reaction was still clearly present in March, 1934.

Case 30.—Personal Case C. A married woman, aged 40, was examined by one of us on March 1, 1934. She said that she was involved in a motor car collision on November 4, 1932. She was thrown forwards and struck her head violently against the steering wheel. She was rendered unconscious immediately, and sustained three deep vertical wounds in the centre of the forehead and above the left eyebrow. There was no bleeding from the nose or ears. The exact duration of unconsciousness is not known, but on the fourth day she could speak rationally and could see. The only obvious symptom at this time was severe headache. A few days later, as soon as she was able to take sufficient notice, she complained that her vision was impaired, and that she could neither taste nor smell. Loss of memory extends from fifteen minutes before the accident to several weeks after it. Headaches ceased a few weeks after the accident, and she left hospital. Sense of smell and taste never returned, and her visual difficulty continued. She was conscious of the temporal restriction of her visual fields and she experienced difficulty in estimating the speed and distance of an approaching object, as in judging the distance of the green at golf, and in estimating the position of a cup when pouring tea. Within a few weeks of the accident she began to put on weight rapidly. She had been about 9 st. for many years, and, during the seventeen months since the accident, had increased to 11 st. 10 lb. Since recovering from the immediate effects of the accident the patient's temperament has been altered. Formerly a vigorous and active personality, she now lacks initiative and interest, and is subject to periods of depression. There has been no polyuria since the accident, and menstruation has remained regular.

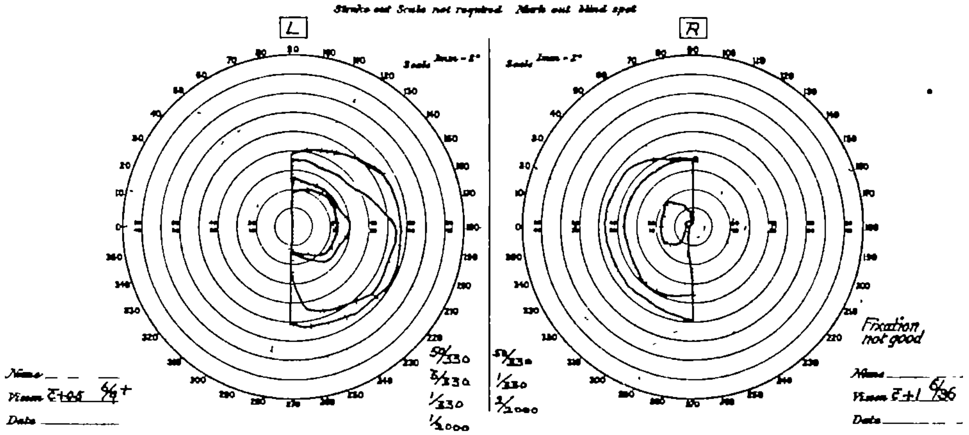

FIG. 3.—Visual fields of Case 30, personal case C.

The patient was of average height and build, and was moderately obese. The scars in the forehead were well healed and there was no underlying irregularity of the bone. X-ray examination was not made. There were no evident mental or intellectual abnormalities. There was complete bilateral anosmia. There was slight pallor of the right optic disc, but the left disc had a normal appearance. Visual acuity was, right: $\frac{6}{36}$, left: $\frac{6}{6}$. There was complete, clean-cut, bitemporal hemianopia, with bisection of the macula on the left, and with a small scotomatous encroachment on the macula on the right side. There was a slight relative depression of the lower nasal quadrant in both fields (fig. 3). The Wernicke pupillary reaction was not tested. The remaining cranial nerves showed no dysfunction and no other abnormalities were discovered.

DISCUSSION.

In view of the great increase in the number of head injuries caused by road accidents, it is surprising that more cases of chiasmal damage have not been reported. One of us (W. R. R.) has personally examined over 450 cases of head injury admitted to Edinburgh Royal Infirmary, and Cases Nos. 28 and 29 are from this series. As others have pointed out, chiasmal damage may escape diagnosis, especially when the visual acuity is little impaired, and when the field defect is slight or transient as in Cases 21 and 24.

The main features of the published cases are indicated in Table I. In twenty-one of the thirty cases the main injury was to the frontal region, in four cases the injury was to the temporal or parietal region, and in the remainder the site of injury was not recorded. The cases described by Griffith and Redslob have been quoted as examples of chiasmal injury following occipital injury. Griffith's case is, however, too indefinite to be included in the series, and in Redslob's case (No. 10) there was a depressed frontal fracture in addition to the occipital injury.

A fall from a height was the commonest cause of the injury (eleven cases). Motor car and motor cycle accidents contributed five of the more recent cases. In accidents such as these the head travelling with great momentum becomes arrested suddenly by a hard surface; such a mechanism produces, not infrequently, the most severe type of head injury.

X-ray examination of the skull was carried out in six cases. None of these showed gross fracture involving the sphenoid, nor did they show displaced fragments of bone in this situation.

Paralysis of one sixth nerve occurred in seven cases, and partial or complete paralysis of one third nerve was reported in seven cases. In one case (No. 22) both third and sixth nerves were damaged; they were affected on opposite sides.

Loss of the sense of smell was reported in five cases.

Impairment of the sense of hearing was present on one side in six cases, and in each of these bleeding from the affected ear had occurred.

Facial paralysis occurred in one case.

Polyuria followed the injury in seven cases. In two of these, Cases 1 and 8, the polyuria passed off within a few months of the injury.

Behr's case (No. 21) and our case (No. 30) developed progressive adiposity without there being any other symptoms of hypothalamic disturbance.

Wernicke's hemianopic pupillary reaction was reported to be positive in nine cases, negative in three, and doubtful in three. Difficulty in testing the reaction may be the cause of this uncertainty. We have found the following method of testing the reaction to be simple and effective. The light of an electric ophthalmoscope is focussed in such a way that on examining the fundus, with the instrument held at a distance of say three inches from the eye, a point of light is seen to focus *on the retina*. Wernicke's reaction can then be tested at any part of the retina by holding the ophthalmoscope at this distance of three inches from the eye in the corresponding part of the visual field. A slight rotation of the instrument is made to direct the focussed light into the eye while the patient maintains fixation on a distant object. It is obviously essential that the light should focus to a point not on the cornea, but on the retina.

Impairment of visual acuity in one or both eyes was usually present. There was complete blindness of one eye in seven cases. In four of these the visual acuity of the other eye was normal. In the remaining 23 cases some vision was present in both eyes. In four, the visual acuity was normal in both eyes. In three, there was normal acuity in one eye, while in 14 cases vision was reduced in both eyes. In two cases the visual acuity was not reported.

The line of the hemianopia bisected the fixation point in eight cases. In sixteen cases there was sparing of the field at the fixation point for a few degrees in the temporal field.

Vision deteriorated gradually in Cases 5 and 12. In Case 16, vision improved in one eye and deteriorated in the other. In the remaining cases, where progress was reported, vision either remained unaltered or improved slightly.

The crossed diplopia which occurred in our first case (No. 28) and in Case 5 is similar to that described by Kubie and Beckmann in cases of bitemporal field defect [20].

PATHOLOGY.

The mechanism by which these chiasmal injuries are produced remains uncertain. Liebrecht [23] considered that a gross division of the chiasma occurred, and described a fatal case in which a tear of the chiasma was found. Koerber [19] also found a tear of the chiasma in a case that died immediately as a result of a very severe injury. In both these cases, however, the injuries were very gross, and are of little value in elucidating the mechanism in patients who survive the injury.

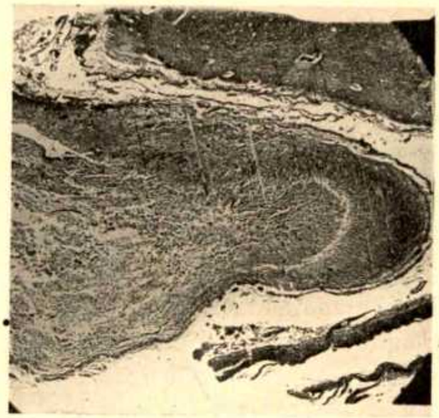

FIG. 4.—Softening of the left half of the optic chiasma.

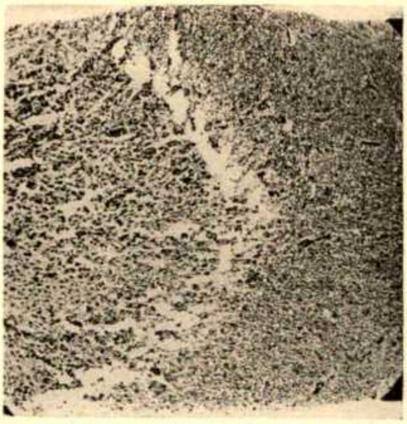

FIG. 5.—Edge of the area of softening in the optic chiasma.

Liebrecht's later case (No. 16) is of importance because death occurred three years after the injury, and an incomplete post-mortem was carried out. The optic nerves and chiasma were found to be atrophic, and an old crack was found in the left orbital plate which continued backwards to the right side of the sphenoid and also to the left optic foramen.

In the type of case we are considering the visual disturbances were caused at the time of the injury, and it is therefore necessary to consider the mechanism by which chiasmal conduction can be suddenly interrupted by violence.

Division of the chiasma by a piece of displaced bone can with confidence be excluded as a cause. The chiasma lies at least one centimetre above and behind the optic groove, and in no case has there been evidence of gross bony displacement in this situation. Sudden stretching of the chiasma by forcible separation of the optic foramina has been suggested as a cause by Coppez [5]. An extensive antero-posterior fracture in the centre of the base of the skull would, however, be necessary for any movement of this nature to occur. There is no evidence that a fracture of this type occurs in these cases, and this idea would not explain those cases which result from violence directed to the lateral aspect of the skull.

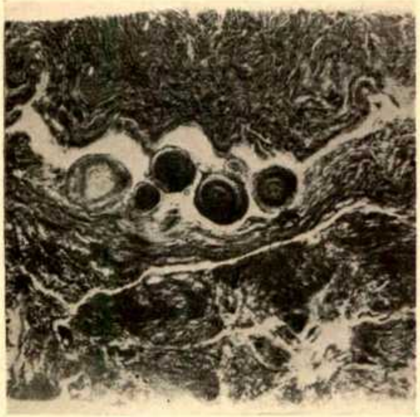

FIG. 6.—Obliterated vessels in the optic nerve sheath.

There is therefore little evidence to support the view that a direct tear of the chiasma occurs, and the only obvious alternative explanation is that the injury interrupts the vascular supply to the chiasma and so impairs its conductivity.

The chiasma is supplied by a rich network of vessels derived from the internal carotid arteries and their branches. These vessels at their origin are firmly fixed to the base of the skull, and any movement of the brain and chiasma relative to the skull may result in the tearing of these small vessels. The probable importance of the movement of the brain relative to the skull in the production of certain brain injuries has been emphasized by one of us [30]. The occurrence of vascular injury seems, therefore, to provide a probable explanation of the mechanism by which the conductivity of the chiasma is injured in these cases. One of us (H. M. T.) has previously come to a somewhat similar conclusion with regard to the mechanism by which the optic nerve is injured in head injuries. The tearing of pial vessels which supply the hypothalamus and tuber cinereum will readily explain the occasional occurrence of polyuria and adiposity in these cases [2].

The important part which vascular damage may play in the production of chiasmal softening is suggested by the following case. One of us (N.M.D) removed a small suprasellar meningioma on September 10, 1933, from a woman aged 63. The patient was also afflicted with a marked degree of generalized arteriosclerosis, the retinal vessels being conspicuously thickened and the systolic blood-pressure being 180 mm. Before operation there was incomplete bitemporal hemianopia and vision was only moderately impaired. The operation was carried out without difficulty, and only very slight manipulation of the optic chiasma was necessary. After recovery from the operation, however, the patient was found to have lost all vision in both eyes. An accidental fall about a month after the operation caused death. At post-mortem examination there was no definite naked-eye abnormality of the visual paths, but microscopic examination showed extensive softening of the chiasma and optic nerves. There was also gross thickening and degeneration of the arteries supplying the chiasma and optic nerves (figs. 4, 5, and 6). It seems probable in this case that slight operative trauma caused thrombosis of the diseased arteries supplying the chiasma and optic nerves. We suggest that in traumatic cases tearing of the chiasmal vessels can produce a similar interruption of function and softening of the chiasma.

It is interesting to compare the visual field changes which occur in traumatic cases with those which occur when the chiasma is pressed upon by a tumour from below. In the latter case the field changes tend to occur in a regular sequence; the upper outer quadrants fail first, the lower outer quadrants next, the lower nasal quadrants third in order and the upper nasal quadrants last. The failure of the fields tends, therefore, to occur in a clockwise direction in the right field, and in a counter-clockwise direction in the left field. The perimetric charts of our three traumatic cases show that there is a tendency for the fields to be involved in similar way to the above. This is shown by the defects of the lower nasal fields in figs. 1 and 3; and also in the preservation of the lower temporal field in fig. 2. Another feature of the fields which may be seen in tumour cases is the persistence of an island of vision in the temporal field which is usually situated on or slightly below the horizontal meridian. This may be the last part of the temporal field to disappear in cases of tumour pressing on the chiasma. In Case 16 of the present series which was reported by Liebrecht, a temporal island of this type was present in both fields (fig. 7). In

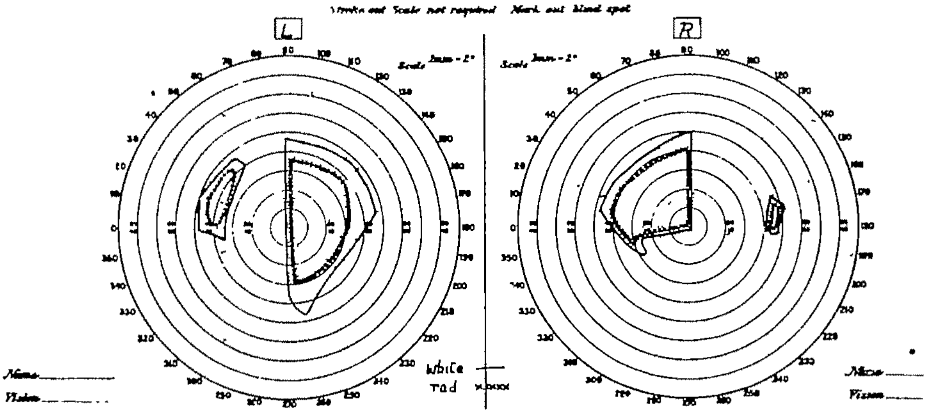

FIG. 7—Visual fields of Case 16, Liebrecht's case A.

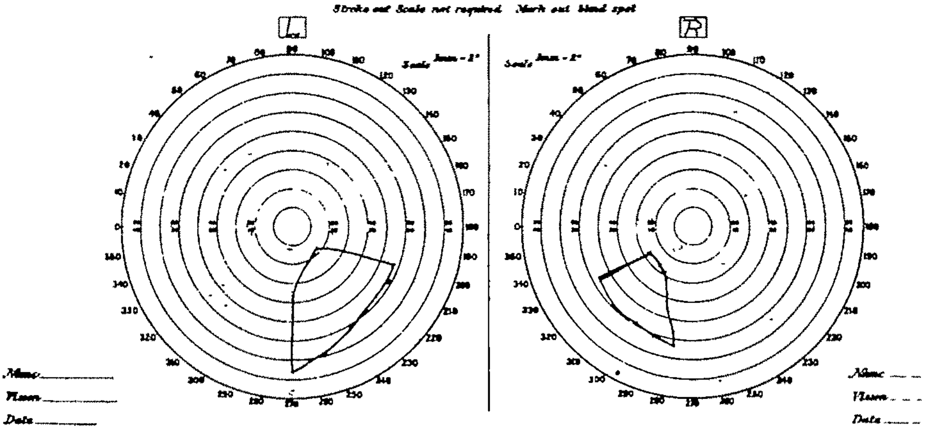

FIG. 8.—Visual fields of Case 18, Liebrecht's case C.

Case 18 there were unusual field changes (fig. 8), of a type which have been described in cases of pituitary tumour [14].

There is, therefore, much resemblance between the field changes which occur in injury and in tumour cases. This suggests that the mechanism of chiasmal injury in tumour and traumatic cases is similar. If the possible mechanisms by which the chiasma may be damaged in traumatic and tumour cases are considered, the obvious factor common to both is that, in each type of case, the vascular supply of the chiasma is impaired. In the traumatic cases this is probably effected by violent rupture of some of the vessels, followed by surrounding local thrombosis and softening. In tumour cases a similar result is brought about by more gradual stretching and final obliteration of the same vessels. It seems therefore probable that in both tumour and traumatic cases, the interruption of conduction in the chiasma is dependent mainly on a gradual or abrupt impairment of its blood supply.

SUMMARY.

The published cases of chiasmal injury have been abstracted, and three further cases have been described.

The clinical features of the cases, and the associated cerebral disturbances which may occur, have been considered.

The visual field changes have been compared with those which occur in cases of tumour pressing on the chiasma.

The mechanism of chiasmal injury has been discussed, and it has been suggested that, in both traumatic and tumour cases, the primary damage is to the vessels supplying the chiasma.

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REACTIONS OF A DOG AFTER REMOVAL OF THE CEREBRAL HEMISPHERES.

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THE experiments were carried out on a young male dog weighing 13·5 kg., " Zavetny " by name. His cerebral hemispheres were removed by two successive operations, the right hemisphere on April 1, 1930, the left on May 27, 1930. The operations were carried out without great loss of blood, and thus it was possible to remove the hemispheres without damaging the subcortical matter.

On April 24, 1930, the gastric and salivary (left parotid) fistulæ were made.

The dog began to walk on the third day after the second operation. At first he walked in circles, leftwards, throwing up his front paws high when he was moving fast, shuffling them along the floor when he was moving slowly. When attempting to shake himself the dog sometimes fell. By the beginning of August all these motor disturbances had disappeared.

" Zavetny " also began to eat on the third day after the second operation. However, he never seized his food, but licked it up slowly. His ration consisted of 400 c.c. of milk, 200 grm. of bread, 100 grm. of raw meat, 300 grm. of cooked oats and a tablespoonful of cod-liver oil, all mixed together. The quantity was given him twice a day, but he would not eat it in the beginning, and what he left was introduced via the fistula into his stomach. Gradually he began to eat more, and three months after the last operation was able to finish off his rations. In the last six months of his life he ate in the normal way, that is, seized his food, and not merely licked it up. However, " Zavetny " never learned to find his food; the basin containing food had to be brought close to his nose for him to take it.

With these rations " Zavetny " kept his weight and looked fit and well, and had an excellent coat, which showed that he was in good physical condition.

The experiment of March 26, 1931, may serve as an illustration of unconditioned alimentary activity. To the stimulus of food consisting of 5 grm. of meat-and-bread powder, his first salivary response was 35 drops, his second 31 drops. After pouring 10 c.c. of 0·25 per cent. hydrochloric acid into his mouth, the salivary response via the parotid fistula was 62 drops. Such quantities are characteristic of normal dogs.

To compare the proportionate periods of sleep and wakefulness of "Zavetny" with those of normal dogs, we put him under continuous observation for several days and nights. The normal "control" dogs slept on the average sixteen hours out of twenty-four. Sleep generally took place at night and in the evening with interruptions occurring every two to three hours, sometimes more often. During these short waking periods the dogs changed their position, scratched or licked themselves and sometimes urinated or defæcated. "Zavetny" slept also mostly at night and in the evening, but he was different from normal dogs in that he slept sometimes for seven to seven and a half hours without changing his position. It was difficult to rouse him even by loud noises, while normal dogs were roused instantly by the sound of our steps. This points again to the greater sensitiveness of the cerebral cortex to external and internal stimuli when compared with the subcortical matter.

His total period of sleep per twenty-four hours sometimes equalled that of normal dogs, sometimes it was as little as eight hours out of twenty-four. In such cases the waking state occupied sixteen hours, a feature that reminds one of Goltz's dog whose rest-and-sleep periods were considerably reduced as compared with normal dogs.

In addition to these prolonged periods of continuous observation we also observed "Zavetny" for many hours during our experiments on the extinction of the orientation reflex. As a rule the dog remained awake during the first half of the day. He walked about the room in every direction, sometimes running from wall to wall, sometimes scratching the door, barking or whining in an unusual manner. The transition from wakefulness to sleep took place gradually. "Zavetny" would begin to walk more slowly and to stop more often, thrusting his nose into a corner or against a wall; he would close his eyes now and again, then his front paws would slide apart and the animal would sit down slowly. Having sat in this position for one to five minutes he would suddenly relax and his body would slip into a lying position, mostly on its belly or on its side with legs stretched out, more rarely curled up. There never was any attempt to find or choose a place to lie down. During the first two-thirds of his life without hemispheres "Zavetny" as a rule slept soundly and in comfortable positions, but in the last few months such postures were not observed. On the contrary the dog slept in surprisingly uncomfortable positions, such as lying on his belly with paws stretched forward and apart, his nose thrust into the floor, or sometimes with his head thrown backwards in a most unnatural way.

The transition from sleep to wakefulness took place instantaneously; the animal rose to his feet with ease and speed. When pushed over on to the floor "Zavetny" got up at once.

In the autumn of 1930 (September 9) and in the spring of 1931 (May 18) we brought "Zavetny" into contact with a bitch on heat. He followed her persistently, licking her, biting her lightly, sometimes standing tensely and even trying to clutch her with his front paws in various places (front, side and back), but no erection took place.

His temperature regulating function remained normal. Goltz mentions that his dog felt warmer to the touch than normal dogs. We experienced the same sensation to our hands when touching "Zavetny," but his temperature, which we took frequently, remained between 39·1° and 39·8° C. The majority of normal dogs have an average temperature of about 38·5° C. (small dogs have higher temperatures). It is possible that a hemisphereless dog loses more warmth during sleep than normal dogs do, as he sleeps stretched out and not curled up. In this case it is intelligible why he should have had a slightly higher temperature than normal. The cooling of the dog (February 27, 1931) in the street at a temperature of 10° C. for half an hour raised his temperature in the room from 39·7° to 40° C. The cooling of Goltz's dog was followed by a drop in body temperature.

"Zavetny" was not guided by vision. When moving about the room he walked into walls as if there were nothing in front of him, touched them with his front paws or nose, and only then changed his direction. In a large room with furniture he invariably walked into obstacles, and if his feet or head got entangled and stuck in an uncomfortable position, he did not try to free himself by a series of co-ordinated movements like a normal dog, but disentangled himself eventually after many fruitless attempts merely by accident, because in the mass of his disorganized movements there happened to be some which effected his release. If the dog, being hungry, accidentally walked into a basin of food, he would bite the edge of the basin until his nose came in contact with the food.

The pupillary reflex took place when light was thrown into the dog's eyes.

His taste reactions were normal: he immediately rejected meat damped with a solution of quinine, and would not drink milk containing 0·1 per cent. of quinine, 5 per cent. of common salt or 5 per cent. of Liebich extract. Though movements of the head occurred which could be described as "seeking" or "sniffing" reactions, "Zavetny" failed to find pieces of meat placed in front of him even when he trod upon them. When "Zavetny" was demonstrated at Professor Orbeli's lecture and a piece of sausage was dangled in front of his nose, no reaction followed, but when the sausage was brought close to his lips, he ate it with an obvious appetite. As a rule the olfactory lobes are destroyed at the removal of the cerebral hemispheres, and the above facts seem to confirm this.

With regard to cutaneous sensibility, besides his failure to find meat when he trod in it, we observed a lowered thermal sensibility of the skin. When any of the dog's paws were plunged into cold water (+ 3° C.) he made no attempt to remove it until we did so ourselves. In one experiment we held the dog in this position for six minutes. Apparently the cutaneous receptors have suffered as well as those of other senses. Therefore, to speak of hyperæsthesia, postulated by Zeliony, is hardly possible.

Picking the dog up, putting him in the experimental stand, or preventing him from walking about on the floor provoked great excitement on his part and a display of strong motor reactions, panting and salivating, sometimes accompanied by biting and barking. However, he calmed down quickly when interference ceased. This is an illustration of one of the basic instincts—reaction against interference with the freedom of movement. The mechanism of the summation of stimuli in the subcortical matter brings about exaggerated, chaotic motor reactions in the absence of the controlling activity of the cortex.

Touching the hair on the dog's back did not provoke the "shaking" reaction.

The pressure exercised through the skin on the mucous membrane of the cheeks provoked the chewing reflex. The stroking of the skin of the neck towards the chin provoked no yawning reflex, as it did in Goltz's dog. Light stroking elicited no wagging of the tail.

The scratch reflex was present. However, we could not get the "Bahnung reflex" to scratching. Scratching of the root of the tail provoked, as in Goltz's dog, the rhythmical putting out of the tongue and biting. When the dog was held in the air in a vertical position for ten minutes rhythmical flexion and extension of the hind legs began to take place. Pressing on the tail did not inhibit these movements as it did in Goltz's dog. Also in contrast to Goltz's dog "Zavetny" refused to follow us when taken on a lead. He stuck his feet into the ground and retreated backwards.

He urinated in the manner of a female dog.

The orientation reflex was present. Cutting paper with a knife or winding a stop watch in the passage adjoining "Zavetny's" room caused him to raise his head and prick up his ears. We carried out several experiments on the extinction of the orientation reflex to various sounds (electric bell, baby's rattle, toy-horn). These experiments took place at 11 to 12 in the morning, either before or an hour after feeding. The stimulus lasted five seconds and was applied at one-minute intervals. As a rule the orientation reflex was absent more frequently when the dog was full than when he was hungry. After meals the animal was usually quiet and often fell asleep. But the repetition of the experiments brought about uniformity of behaviour, and the differences gradually disappeared. The percentage of the absence of orientation reflex became the same in the satiate as in the hungry state. This might be interpreted as an indication of the extinction of the orientation reflex.

The following table illustrates this :—

Date	Stimuli	Total No. of stimuli	No. of stimulus at which extinction began	No. of stimuli which provoked no response	Per cent. of stimuli which provoked no response	Remarks
1930						
5.12	Bell.. ..	126	55	39	31	The dog was fed before experiment.
15.12	Rattle ..	106	88	9	8·5	The dog was not fed.
28.12	Rattle ..	70	12	39	56	,, was fed.
30.12	Rattle ..	80	18	26	32·5	,, was not fed.
1931						
7 5	Horn ..	83	45	42	51	,, was fed.
9.5	Rattle ..	57	24	28	42	,, ,, In the last two experiments the dog remained wide awake after feeding.

The extinction of the orientation reflex was brought down to two or three noughts, that is, if no orientation reflex was provoked by two to three consecutive stimuli, we regarded it as extinguished. If after this a new stimulus was applied, the orientation reflex generally reappeared.

The extinguishing of the orientation reflex and training in the process of inhibition, which is clear from the table in the case of rattle, are properties of cortical activity. These experiments made it clear that some part of the cortex had not been removed and continued to function. It also made intelligible the establishing in " Zavetny " of a conditioned salivary reflex to a metronome. However, the establishing of this reflex took a long time. It appeared first at the 250th application as 3 drops, during thirty seconds of the isolated application of the stimulus. One of these experiments demonstrating "Zavetny's" conditioned reflex was done in the presence of Professor Pavlov (on May 12, 1931) and was a complete success. But even earlier, in December, 1930, we noticed " Zavetny " standing up on his hind legs and scratching the door leading into the passage where he was usually fed when we approached that door in the morning, and he could hear our steps outside. We had never seen him before standing up on his hind legs or scratching the walls, and for a long time could not understand this behaviour. The establishing of a conditioned reflex to the metronome explains it, however, as another alimentary conditioned reflex established to the sound of footsteps.

On April 15, 1931 " Zavetny " had his second fit of convulsions of a clonic type. On May 29, 1931, a third fit of the same kind occurred which ended in the dog's death. Thus " Zavetny " lived without cerebral hemispheres for one year and two days. The weight of his corpse was 13·2 kg. The autopsy and macroscopic examinations were carried out by Professor A. D. Speransky to whom we are grateful. The dura mater was found adhering closely everywhere to the remnants of the brain tissue. It was very much thicker than normal, especially at the posterior near the tentorium cerebelli, as well as along the middle line above the fissura cerebri magna where the thickness of the scar exceeded 1 cm. On its internal surface the dura mater adhered closely to the surface exposed by the removal of the cerebral hemispheres. There were no scars on the base of the brain. Scars were found in front, in the region of the olfactory lobes, which were destroyed by the operations. All the nerves of the base of the brain were intact and were not adherent to scar tissue.

Transversal sections made from the medulla oblongata to the front end of tractus olfactorius at a distance of 2 to 3 mm. from one another have shown: (1) The lower posterior horn of the left lateral ventricle was absent to the middle of the thalamus; (2) in that part the dura mater modified by the scar adhered directly to the subcortical matter; (3) owing to the secondary scar formations the cornu ammonii on the left . . . was hardly discernible; (4) in front of their middle parts both lateral ventricles were intact and descended together with the fornix towards the front part of the base of the brain; (5) the right gyrus pyriformis was intact, the left was damaged; (6) near the right gyrus pyriformis we found a well preserved portion of the auditory area of the cortex-gyrus compositus posterior. The rest of the brain presented no noticeable changes.

In conclusion we should like to add that some of Goltz's assumptions were confirmed by the examination of "Zavetny," i.e. that hemisphereless dogs with or without minor damages to the subcortical matter retain more function and in a better state than has happened in the case of his dog. The same is confirmed by Zeliony's dog, which retained his play reflex after his cerebral hemispheres were removed, and which had a larger portion of the subcortical matter than Goltz's dog.

SUMMARY.

(1) A small portion of cerebral cortex is sufficient for the establishing of simple conditioned reflexes.

(2) Motor disturbances in hemisphereless dogs pass away almost completely in the course of time.

(3) The sleep of hemisphereless dogs is deeper and sounder than that of normal dogs, owing to the absence of the cerebral cortex, which is a more sensitive mechanism to internal and external stimuli than the subcortical matter.

(4) All the internal functions of the organism (metabolism, temperature regulation, &c.) depending upon the subcortex remain satisfactory in hemisphereless dogs.

(5) Hemisphereless dogs lose sight and smell. Taste remains more or less normal.

(6) Cutaneous sensibility to mechanical and thermal stimuli is lowered.

(7) The unconditioned orientation reflex to sounds and noises is preserved.

(8) Exploratory (investigatory (reactions) movements of the head) are preserved, and can be easily mistaken for olfactory reactions which in reality are absent.

(9) The mating (sex) instinct in hemisphereless dogs may be preserved but incompletely.

(10) Hemisphereless dogs are unable to find their food without assistance.

(11) We have never observed in "Zavetny" fits or convulsions of the tonic type.

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NOTICES OF RECENT PUBLICATIONS.

Nouveau Traité de Médecine. Fascicule XX. Pathologie du Système Nerveux. (Bulbe, Nerfs craniens, Méninges, Moelle.) Paris: Masson et Cie, 1935. Pp. 984. Price 130 fr.

This volume completes the system of medicine which has been appearing for some years under the auspices of Professors Roger, Widal and Teissier. Of the twenty-two volumes four have been devoted to diseases of the nervous system. Unfortunately several years have elapsed since the publication of the first of these, and consequently the system as a whole scarcely presents an up-to-date picture of neurology of to-day. Even in the volume under review there are indications that some of the articles were written some time ago; that on diseases of the meninges was originally prepared by Sicard who died some years ago, and in other chapters there is a failure to note recent advances in knowledge, as in that on the sphincters, myasthenia gravis and the combined degenerations of the cord. But on the whole this volume, as its predecessors, is an admirable presentation of clinical neurology in which special emphasis is laid on symptoms and diagnosis in which the French school has always excelled.

The first quarter of the volume is devoted by Guillain and Alajouanine to diseases of the brain-stem; it is an excellent presentation of the subject, complete, concise, well arranged and adequately illustrated. It is, of course, largely concerned with local lesions, but the resulting symptoms are carefully analysed and diffuse and systemic affections, as polio-encephalitis, bulbar palsy and other diseases, are also dealt with. Froment describes fully diseases of the cranial nerves; his chapter on facial spasms is particularly interesting. The article in which he collaborates with Colrat on the optic nerve is less satisfactory. Sicard's contribution on the meninges, which has been revised by Haguenau, includes sections on the aseptic meningitides and on subdural and subarachnoid hæmorrhage. The symptoms of spinal compression and their pathology are described by Léri and Thiers, and other chapters deal with spinal concussion, hæmatomyelia, abscess of the cord and acute myelitis.

The same authors, in collaboration with Lièvre, discuss fully all aspects of tabes dorsalis and its treatment. The chapter on the combined degeneration of the cord by Crouzon is disappointing; sufficient space has not been allotted to it, and recent work and experiences on subacute combined degeneration do not receive the notice they deserve. Léri and Thiers also write on spinal muscular atrophy, amyotrophic lateral sclerosis and disseminated sclerosis, and Alajouanine on syringomyelia. The chapter on syphilis of the cord is scrappy and unsatisfactory.

Lehrbuch der Nerven-und Geisteskrankheiten. Herausgegeben von Professor W. WEYGANDT. Halle a. S.: Carl Marhold. 1935. S. 663. Price 24.80 RM.

In a short introduction to this textbook Professor Rüdin emphasizes the importance to the student, the physician and to the State of dealing with the biological and hereditary aspects of nervous and mental diseases, and in the preface the editor also insists on the necessity of treating these conditions from the social and eugenic as well as from the clinical and individual standpoint. But though attention is focused on these important aspects, the reader will find that the treatment and discussion of nervous and mental disorders follows more or less conventional lines, though most of the authors succeed in impressing their personal views and experiences on the subjects on which they write.

The long introductory chapters in which the ætiology, symptoms, psychical and somatic pathology, and the treatment of nervous and mental diseases are considered together is a striking feature of the book; this is a most praiseworthy method, as valuable to the neurologist as to the psychiatrist, as it helps to bring together two branches of nervous disease which have been too generally separated. In the clinical sections disorders of various systems and individual diseases are concisely but clearly described and discussed. The illustrations are not numerous, but are well chosen, and there is an excellent index.

Diseases of the Nervous System: A Textbook of Neurology and Psychiatry. By SMITH ELY JELLIFFE and WILLIAM H. WHITE. Sixth Edition. Pp. 1175. 1935. London: H. K. Lewis and Co. Price £2 2s.

The appearance of the sixth edition of this textbook, which was first published twenty years ago, is evidence of its popularity. It has been revised and in parts rewritten, but its essential features remain unchanged; the first part deals with conditions which are generally regarded as neurological, the second, of 260 pages, with the neuroses, psychoneuroses and psychoses under the title "psychical or symbolic systems." In the latter section the subjects are treated on more or less conventional lines, but from a rather extreme psychoanalytic angle. The most striking features of the earlier chapters are the importance given to disorders of the autonomic systems and to disturbances in the functions of the endocrine organs in the ætiology and manifestations of nervous diseases and the large rôle which psychogenic factors are assumed to play in pathogenesis. Any new point of view is valuable if it is based on adequate facts, but it is difficult to accept many statements found in these chapters, particularly without more evidence than the authors present, and to follow certain of their arguments. Gastric and duodenal ulcers, for instance, are attributed to a "malignant psychogenic maladjustment, hyperadrenalemia with later exhaustion"; psychical factors are assumed to play a part in the production of myasthenia gravis, and psychotherapy is recommended as one of its important therapeutic agents, and myotonia is due to defective parasympathetic control raising the threshold of the synapse and thus preventing the immediate passage of the voluntary stimulus.

The main features of the organic diseases of the nervous system are, however, excellently presented, their ætiology and pathology are clearly discussed. Here the extensive experiences of the authors and their intimate acquaintance with the literature are evident and both are happily blended.

Though not a book for the student it should prove useful and stimulating to the practitioner and neurologist.

Tumeurs de L'Encéphale. Par D. PAULAIN. Paris: Masson et Cie. 1935. Pp. 216. Price fr. 30.

There is little which distinguishes this monograph from the numerous books which have appeared during the last few years on cerebral tumours. It is based on forty-six cases observed in Bucharest during the past ten years, clinical and pathological details of all of which are given. As post-mortem examinations were available in almost all the correlation of the clinical and autopsy findings would have been instructive if the clinical descriptions were more complete. The chapter on the pathology of tumours presents nothing new. There are numerous illustrations, but the reproduction of many of them is not satisfactory.

Hughlings Jackson Memorial Volume. Edited by Professor L. BENEDEK. Published by the Clinic for Nervous and Mental Diseases, Debrecen, Hungary. 1935.

In celebration of the centenary of Hughlings Jackson's birth the members of the Clinic for Nervous and Mental Diseases of the University of Debrecen, have collected a large number of their papers into this volume which has been edited by their Director, Professor Ladislaw Benedek, who has also contributed to it a sympathetic appreciation of Jackson's work. The articles, many of which have been published elsewhere, are arranged according to the subjects with which they deal. The first section on psychiatric subjects includes nine papers, of which the most interesting perhaps is Professor Benedek's on the effect of active immunization of patients suffering with nervous syphilis by non-pathogenic *Spirochæta pallida*. In another section seven contributions on psychology and psychopathology are brought together, and this is followed by a few papers on eugenic and hereditary problems. Among these is included a valuable review by Benedek on the relation of the traumatic neuroses to cerebral commotion. But the majority of the fifty-seven papers which this volume contains are devoted to neurological subjects, and much valuable work is contained in them.

The volume is not only a valuable collection of papers but also an indication of the clinical and scientific activity of an important centre of neurology and psychiatry; it is also welcome as a token of a friendly spirit of international interest.

The Anatomy of the Nervous System. By S. W. Ranson. Fifth Edition. Philadelphia and London: W. B. Saunders and Co., Ltd. 1935. Pp. 501, with 381 illustrations. Price 27s. 6d.

Since it first appeared in 1900 this textbook on the anatomy of the nervous system has proved its worth and acquired the popularity with teachers and students which it rightly deserves. It was originally so well planned and so complete within the limits intended by the author, that little change has been necessary in subsequent editions, though new facts or conceptions significant from the aspect of structure or function have been where necessary included. This has necessitated considerable revision in the present edition, but the chief addition to it is the inclusion of a series of illustrations of the fibre masses and nuclei as seen in sections of brain-stem and fore-brain at the end of the volume; these constitute a comprehensive atlas which will be extremely valuable for reference as well as for the student, more particularly as the more important structures in each section are fully described in the accompanying text and their significance pointed out.

The value of this textbook for the clinical student is that it is, as the author claims, "written from the standpoint of development and function," by one well fitted to do so; in this respect it contrasts with many textbooks in which anatomical facts are recorded without reference to their functional or clinical significance.

Clinical Aspects of Visceral Neurology. By W. K. Livingston. London: Baillière, Tindall and Cox. 1935. Pp. 254. Price 22s. 6d.

The book opens with a section devoted to the anatomy of the visceral nervous system and to the many physiological hypotheses now current in connection with it. The pharmacology of the system and the problem of visceral pain are also fully considered.

Part two deals with those clinical conditions, believed to arise from disease or disordered function of the visceral nervous system, for which visceral nerve resections are performed or proposed. These include occlusive diseases of blood-vessels, angina pectoris, Hirschsprung's disease, disorders of bladder function and dysmenorrhœa. Chronic arthritis appears now to be added to the maladies treated in this way.

This list indicates a tendency, which is not unfamiliar when some new division of the nervous system comes into the forefront of clinical attention, to lay to the charge of the visceral nervous system disorders with which its connection is not yet wholly clear.

Surgical opinion has not been inclined to wait upon the filling of these gaps in our knowledge, and numerous. ingenious and somewhat experimental operative procedures have been devised and performed for these various maladies. It is satisfactory to see that the treatment of spasticity of the skeletal musculature has now finally disappeared from this category, though it must in justice be admitted that the new era of visceral neurosurgery owes its origin to the work of Hunter and Royle in this direction.

The reader will find a comprehensive summary of the literature of the subject, together with detailed accounts of the author's own work and experience. To the surgeon the book will be of especial interest in its technical aspects.

There is an exhaustive bibliography.

Untersuchungen über die Fruchtbarkeit gewisser Gruppen von Geisteskranken. (Acta Psychiatrica et Neurologica. Supplementum VIII.) Von ERIK ESSEN-MÖLLER. Copenhagen. Levin and Munksgaard. 1935. Pp. 314.

The material for this thorough study of fertility among the insane comprised nearly 5,000 cases of manic-depressive insanity, schizophrenia and epilepsy, together with 1,000 normal persons who could be used for comparison. Two years were spent in collecting the data, which have later been submitted to a statistical analysis, here clearly and simply presented. The conclusions reached confirm the general impression of psychiatrists on this matter and are explicable without resort to any hypothesis as to an intrinsic connection between inherited fertility factors and those responsible for the mental illness. Among many interesting data are the figures for the number of children born prior to the first admission to hospital: from these and related statistics it may be recognized how small an effect compulsory sterilization of insane patients would have on the incidence of such illness in the next generation, or even in many succeeding generations.

Kurzgefasstes Lehrbuch der Psychiatrie. Von Johannes Lange. Leipzig: Georg Thieme. 1935. Pp. 254. Price M. 8.70.

This is, in intention and effect, an elementary textbook of psychiatry; as it expressly avoids all discussion of unsolved problems its interest for the advanced psychiatrist is in inverse proportion to its value to the medical student and the general practitioner. Its size and detail are clear indications, however, of the range of assured knowledge in psychiatry, too often overlain by research questions or belittled in favour of speculation. The direct style and orderly, rather dogmatic, presentation are in accordance with the author's modernized Kraepelinian approach to his subject.

Alcohol and Anæsthesia. By W. BURRIDGE. London: Williams and Norgate, Ltd. 1934. Pp. 65. Price 2s. 6d.

An experiment on the perfused heart is here the starting point for a series of loose analogies and views on the nature of neural energy, mental processes, and the action of drugs. The author's style is polemical and diffuse, his terminology novel, and his opinions, especially as regards drug-addiction, hardly justified by the facts and arguments adduced in their support.

Psychometrics, a Study of Psychological Measurements. By JOHNSON O'CONNOR. Cambridge, Massachusetts. Harvard University Press. London: Humphrey Milford: Oxford University Press. 1934. Pp. 292. Price 15s. net.

In this report of a statistical research in psychology, the reliability of a number of tests is brought under review and certain mental elements defined. The criteria employed for definition of a mental element were that it must be measurable, must have a reproducible skill curve and must be independent of age and experience and of other mental elements. The seven mental elements isolated in these experiments are summarized as personality, tonal memory, engineering aptitude, clerical aptitude, tweezer dexterity, finger dexterity and creative imagination. The methods of experiment and of evaluation are fully recorded. The work, admirably precise and technical, is a useful addition to the literature of industrial psychology.

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To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

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THE EFFECT OF INCREASED INTRACRANIAL VENOUS PRESSURE ON THE PRESSURE OF THE CEREBROSPINAL FLUID.

BY T. H. B. BEDFORD.

(From the Department of Pharmacology, Manchester University.)

It has been known for some time that constriction of the veins of the neck is followed by an increase in the pressure of the cerebrospinal fluid. This phenomenon was made use of by Queckenstedt [13] in his test for obstruction of the spinal subarachoid space. Queckenstedt suggested that the rise in the pressure of the cerebrospinal fluid was due to an over-filling of the brain with blood. He thought also that the pressure was perhaps raised in another way. He believed that after compression of the veins of the neck blood escaped from the brain into the venous plexuses which surround the dural coverings of the spinal cord. The vessels of these plexuses would then become distended with blood and exert an abnormal pressure on the dura of the upper cervical cord. This he thought would lead to an increase in the pressure of the cerebrospinal fluid. It is noteworthy that Queckenstedt found it unnecessary to postulate either an increased formation or a delayed absorption of the cerebrospinal fluid to account for the rise of pressure.

Before considering the effect of increased intracranial venous pressure on the pressure of the cerebrospinal fluid it is proposed to consider briefly what is known of the normal relation of the intracranial venous pressure and the cerebrospinal fluid pressure.

The normal relation of the intracranial venous pressure and the cerebrospinal fluid pressure.

The experimental investigation of the subject may be said to have started with the work of Leonard Hill [12] in 1896. Hill attempted to make direct measurements of the two pressures and came to the conclusion that the cerebrospinal fluid pressure and the torcular venous pressure must at all times be equal. Nearly twenty years later Dixon and Halliburton [7] also made direct measurements of the pressures, and expressed the opinion that the cerebrospinal fluid pressure was independent of the venous pressure at the torcular and that of the two the venous pressure was considerably the higher. Wagefarth [14], about the same time, considered that the cerebrospinal fluid and the torcular pressures were not equal but that the cerebrospinal fluid pressure was normally the greater although it was being constantly reduced towards the level of the venous pressure. He came to these conclusions in the following way. An artificial opening was made between the superior longitudinal sinus and the subarachnoid space in dogs, the opening persisted for at least four days. Bleeding from the sinus into the subarachnoid space occurred in only one case and in this animal cerebrospinal fluid had been removed at the time of the puncture. In these animals the removal of anything but the smallest amount of cerebrospinal fluid was followed by marked subdural and subarachnoid hæmorrhage. These experiments would seem to indicate that the cerebrospinal fluid pressure was constantly above that of the superior longitudinal sinus and that blood did not pass from the sinus to the subarachnoid space unless cerebrospinal fluid was withdrawn in a quantity sufficient to alter the intracranial pressure relations.

Frazier and Peet [11] considered that the torcular and the fluid pressures were identical and thus supported the findings of Leonard Hill. A careful investigation of the problem was made by Becht [1] who came to the conclusion that the torcular and the cerebrospinal fluid pressures were almost but not exactly equal and that no definite statement could be made as to which pressure was normally the higher. Weed and Hughson [15], however, by employing an improved method of recording the torcular venous pressure came definitely to the conclusion that "the pressure of the cerebrospinal fluid is not identical with either the sagittal or the brachial venous pressure." They also stated that "in the control experiments and in the initial control periods of other observations, the cerebrospinal fluid pressure has been found to be from 5 to 50 mm. above that of the sinus" and they concluded that under normal conditions the pressure of the cerebrospinal fluid was always higher than the torcular pressure.

In the experiments which are about to be described it was the custom to measure both the torcular and the cerebrospinal fluid pressure during an initial control period. The animals were always in the horizontal position. Although observations were made on many dogs, the torcular pressure was always found to be from 25 to 95 mm. of a 4 per cent. solution of sodium citrate below that of the cerebrospinal fluid.

These observations confirm the finding of Weed and Hughson that the pressure of the cerebrospinal fluid always exceeds that of the torcular, but it should be noted that the difference in the two pressures was occasionally found to be greater than the maximum described by these two workers.

We are now in a position to consider what is known of the effect of obstruction of the venous return from the brain on the pressure of the cerebrospinal fluid.

The effect of obstruction of the venous return from the brain on the pressure of the cerebrospinal fluid.

According to Becht [1], who has reviewed the literature up to 1920, Falkenheim and Naunyn [9] were the first to study the effect of raising the venous pressure on the pressure of the cerebrospinal fluid. A small rubber balloon was placed in the right ventricle of the heart and inflated. In two animals there was a rise in the pressure of the cerebrospinal fluid while in the third animal there was a fall. Falkenheim and Naunyn concluded that the rises in fluid pressure were caused by venous stasis without much reduction in the arterial pressure while the fall was caused by a fall in the arterial pressure due to the marked reduction of cardiac output which was caused by the direct pressure of the balloon. Dixon and Halliburton [7] observed in the course of their experiments that a rise of venous pressure caused a rise in the pressure of the cerebrospinal fluid. They also found that the rise in the pressure of the cerebrospinal fluid was only about one quarter of the rise in the pressure at the torcular. They found, however, that the alterations in the fluid and the venous pressures were neither synchronous nor proportional and they concluded that although the pressure of the cerebrospinal fluid was influenced to a small extent by changes in the venous pressure these alterations were insignificant compared with the independent changes in pressure which occurred as the result of secretory activity. Frazier and Peet [11] found that a fairly constant rise in the pressure of the cerebrospinal fluid followed occlusion of the venous circulation. They concluded that "the more or less constant rise in cerebrospinal fluid pressure when the venous circulation is interrupted confirms the hypothesis that the absorption of cerebrospinal fluid takes place chiefly through the venous channels." A series of experiments was performed by Dandy and Blackfan [5] on dogs, in which they noted the rate of escape of cerebrospinal fluid from a needle in the cisterna magna. They observed an instantaneous and marked increase in the outflow of cerebrospinal fluid on compressing the jugular veins. They state: "This increased production (of cerebrospinal fluid), however, disappears within a few minutes as the collateral venous circulation becomes established" and later they express the opinion that the increased outflow of cerebrospinal fluid can be explained only by an increased production of fluid.

Much of our knowledge of the nature of the initial effects of compression of the jugular veins upon the pressure of the cerebrospinal fluid is due to the work of Becht [1]. This worker's experiments provide fairly conclusive evidence that the sudden increase in the pressure of the cerebrospinal fluid which follows compression of the vessels of the neck is caused neither by an increased production nor by a delayed absorption of the cerebrospinal fluid, but that it is due to an accumulation of venous blood in the cranial cavity and a displacement of the cerebrospinal fluid into the spinal canal. Becht came to these conclusions as a result of the following observations: (1) He found that the changes in the fluid and the torcular pressures observed on compression and on release of the veins of the neck varied in the same direction and ran a remarkably parallel course. It was evident from these observations that one of the factors which determined the pressure of the cerebrospinal fluid was the venous pressure in the skull. (2) He raised the pressure of the cerebrospinal fluid to a constant height: (*a*) By introducing saline solution into the subarachnoid space through a needle in the cisterna magna; (*b*) by a temporary ligation of the external jugular veins. He then determined the time required for the pressures to return to their original levels. The time required for the fall of pressure after the introduction of saline was nearly thirty times as long as that after release of the jugular veins. Further, the rise of pressure in the former instance was unaccompanied by a rise in the pressure at the torcular while in the latter it was accompanied by an increase in the torcular pressure. In one of his experiments, six minutes were required before the pressure of the cerebrospinal fluid which had been raised by the introduction of saline solution returned to its original level while a pressure of equal height which had been produced by constriction of the external jugular veins returned to its original level in eleven seconds when these vessels were released. Becht considered that if an actual increase in the quantity of cerebrospinal fluid had resulted from ligation of the jugular veins, a longer period than eleven seconds would have been required for readjustment after release of the veins. Becht's observations on the effect of ligation of the jugular veins on the pressure of the cerebrospinal fluid have been confirmed and extended by Weed and his co-workers. Weed's [16] conclusions are summarized in the following extract from a paper entitled " The relation of the intracranial pressures " which he published in collaboration with Flexner in 1933 : " Increase in the cerebral venous pressure as effected by pressure upon the veins of the neck of the animal results in a prompt rise in the pressure of the cerebrospinal fluid but always to a lesser extent (than the rise in venous pressure). Eleven experiments in our series yielded an average increase of 267 mm. in cerebral venous pressure and 176 mm. in cerebrospinal fluid pressure, indicating that 65 per cent. of the venous pressure increase is reflected in the pressure of the fluid. If, however, the data are taken from levels at which the pressure of the cerebrospinal fluid is raised but slightly over 100 mm. (as in the case of head-down tilting), the average increase becomes 178 mm. for the sagittal sinus and 112 mm. for the cerebrospinal fluid. Hence within this normal range of pressure-change, 63 per cent. of a sagittal pressure increase is reflected upon the cerebrospinal fluid." Weed, however, was mainly concerned with the investigation of the factors responsible for the changes in cerebrospinal fluid pressure which occur on the abrupt alteration of the animal's position. It is not proposed to consider this aspect of the subject in this communication.

With the possible exception of Dandy and Blackfan, the investigators whose work has just been described appear to have been concerned mainly with the effect on cerebrospinal fluid pressure of a sudden and temporary occlusion of the veins of the neck and to have made little attempt to determine the effect of prolonged venous obstruction. Allusion has already been made to Dandy and Blackfan's experiments. Their conclusions have been severely criticised by Becht [1] and by Weed [15] who have pointed out that their experimental findings can readily be explained without postulating a new formation of cerebrospinal fluid. Similarly their conclusion that the falling off of the initial outflow of fluid which was found to occur during prolonged compression of the jugular veins coincided with the establishment of collateral circulation, appears to have been mainly speculative, for they record no measurements of the intracranial venous pressure.

In a paper which appeared in 1919, Dandy [6] re-stated his views in the following terms : " Whether hydrocephalus results from venous stasis depends entirely upon the amount of collateral circulation which can develop. If both jugular veins are compressed in a dog, the amount of cerebrospinal fluid is immediately and rapidly increased. The increased production, however, disappears within a few minutes as the collateral circulation becomes established." Flexner and Winters [10] determined the rate of flow of cerebrospinal fluid from the aqueduct of the cat. They maintained the cerebrospinal fluid at a constant pressure of 110 mm. water throughout the experiments. In several of the experiments the cerebral venous pressure was also recorded by a cannula in the peripheral end of an external jugular vein. Certain deviations from a constant rate of flow of cerebrospinal fluid were correlated with intracranial venous pressure changes and were considered to provide evidence of changes in the ventricular volume. No observations, however, are recorded of the influence of a prolonged increase of intracranial venous pressure on the flow of cerebrospinal fluid.

Although the effect on the cerebrospinal fluid pressure of an abrupt and temporary increase in the intracranial venous pressure seems now to have been determined with accuracy, little or no work is available concerning the influence of a prolonged state of raised intracranial venous pressure. It may, indeed, be claimed that although the initial rapid rise in the pressure of the cerebrospinal fluid is caused by an increase in the volume of the intracranial venous system and not by an increase in the quantity of the cerebrospinal fluid, a prolonged state of raised intracranial venous pressure may nevertheless lead to the accumulation of cerebrospinal fluid. This could be effected in one or both of the following ways: (*a*) the raised intracapillary pressure of the choroid plexuses may lead to an increased filtration of cerebrospinal fluid if simple filtration is the process by which cerebrospinal fluid is normally formed; (*b*) the raised blood-pressure in the intracranial venous sinuses may cause a delay in the rate of absorption of the cerebrospinal fluid and provided the rate of formation remains constant cerebrospinal fluid may tend to accumulate in the subarachnoid space. A criticism of the first of these possibilities has been presented in an earlier paper [2]. It is apparent, however, from the following extracts, which are taken from "Recent Advances in Neurology" (1934), by Brain and Strauss, that both these views are not lacking in supporters. On page 8 the authors state: " . . . a general rise of intracranial venous pressure, however, is a frequent accompaniment of cerebral tumour and this may contribute to the development of hydrocephalus by leading to an increased formation of cerebrospinal fluid, since a general rise of intracranial venous pressure would involve not only the vein of Galen but also its collaterals," and later on page 12: "An abnormally high blood-pressure in the intracranial venous sinuses diminishes the absorption of cerebrospinal fluid by increasing the force opposing the passage of the fluid through the arachnoid villi. A cerebral tumour which presses upon venous sinuses may thus in yet another fashion contribute to the development of hydrocephalus."

The experiments which are to be described were undertaken in an attempt to determine the influence of a prolonged state of increased intracranial venous pressure upon the pressure of the cerebrospinal fluid. As it was necessary in some of the experiments to place obstructions on the course of the intracranial venous sinuses, it is proposed first to describe the anatomy of the intracranial venous system of the dog.

The intracranial venous system of the dog.

A search through the available literature has failed to reveal any account of the intracranial venous system of the dog other than that by Ellenberger and Baum [8]. As the description given by these authors was found to be incomplete and to contain a number of inaccuracies it was decided to restudy the whole system. For this purpose a number of dogs' heads were prepared for dissection by the injection of the venous system with carmine gelatine solution. The method employed has already been described in an earlier paper [3].

Almost the whole of the blood from the convexity and the greater part of the blood from the inner aspect of the cerebral hemispheres drain into the superior longitudinal sinus. It will be observed from fig. 1 that the sinus, on reaching the torcular Herophili, divides its blood equally between the right and the left lateral sinuses. Just before terminating the superior longitudinal sinus enters a canal in the substance of the occipital bone. The torcular and the inner third or more of the lateral sinuses are also situated within the bone. The straight sinus enters the torcular through a foramen in the upper part of its anterior wall. For details of the Galenic system of the dog reference should be made to an earlier paper [2]. The lateral sinus follows a course which corresponds fairly closely with that found in man until it reaches the posterior border of the petrous portion of the temporal bone. Here the sinus runs forwards and downwards in the substance of the temporal bone and emerges from the skull through the postglenoid foramen which is situated directly behind the postglenoid process.

Ellenberger and Baum have applied the term "superior cerebral vein" to the sinus after it has left the skull. It is soon joined, however, by the internal maxillary vein and the common trunk so formed unites with the external maxillary vein to form the external jugular vein. The arrangement of the veins in this region is, however, very irregular and a detailed description is unnecessary for the purposes of this communication. It is, of course, well known that in the dog the external jugular vein is a large and well-defined vessel and contrasts with the internal jugular vein which is relatively small. In the dog there is no sigmoid sinus and although Ellenberger and Baum have described a superior petrosal sinus this has not been encountered in any of the specimens which have been examined. Just before the lateral sinus

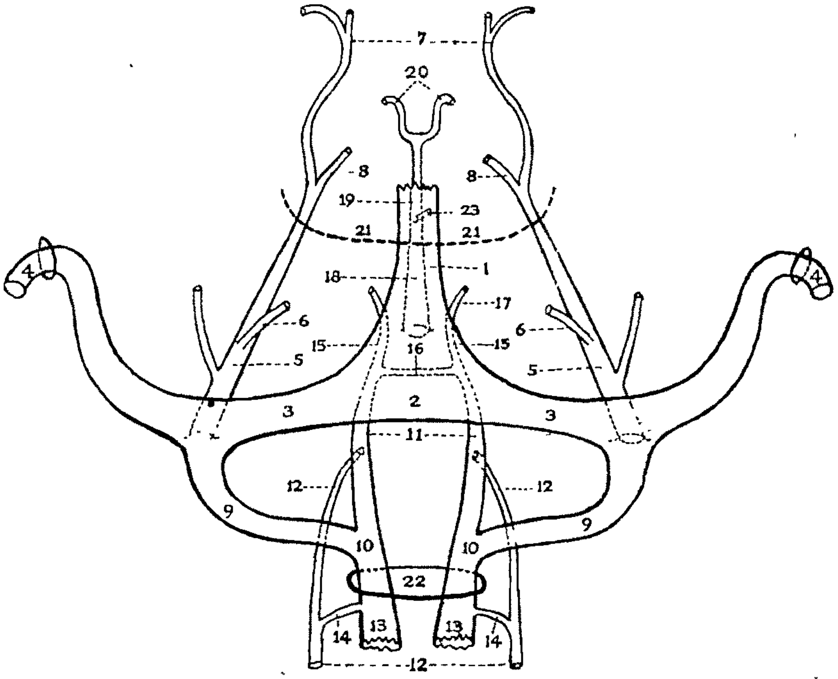

FIG. 1.—Diagrammatic representation of the intracranial blood-sinus system of the dog. The true relations of the various structures have been considerably distorted and the sinuses are depicted as occupying one plane. (1) Superior longitudinal sinus; (2) torcular of Herophili, (3) lateral sinus; (4) postgleniod foramen; (5) basal vein; (6) temporo-occipital tributary of basal vein, (7) anterior cerebral vein; (8) tributary from medulla, pons and cerebellum; (9) superior occipital sinus; (10) inferior occipital sinus; (11) petrosal sinus; (12) internal jugular vein; (13) vein of vertebral column; (14) tributary of internal jugular vein from vein of vertebral column; (15) cavernous sinus; (16) intercavernous sinus; (17) ophthalmic vein; (18) straight sinus; (19) great vein of Galen; (20) vein of Galen; (22) foramen magnum; (21) tentorium cerebelli; (23) inferior longitudinal vein.

reaches the posterior border of the petrous temporal bone, a venous sinus passes directly downwards from its lower border. This is the superior occipital sinus. At first the sinus lies within the dura but it soon enters a canal in the occipital bone and ultimately unites with the petrosal sinus to form the inferior occipital sinus. The anterior wall of that portion of the lateral sinus from which the superior occipital sinus takes origin is not usually ossified. An opening through which blood is received from the basal vein is situated in the region where the superior occipital sinus takes origin. A detailed description of this vessel has been presented in an earlier communication [9]. The basal vein receives blood mainly from: (1) the under surface of the optic lobe through the anterior cerebral vein; (2) the under surface of the temporal and occipital lobes through a large vessel which usually joins the basal vein while the latter lies within the tentorium; (3) a proportion from the island of Reil, the midbrain, the pons, the cerebellum and the choroid plexus of the descending horn. The main function of the vessel, however, appears to be the drainage of blood from the inferior aspect of the cerebral hemispheres. It is noteworthy that the opening where the basal vein terminates in the sinus is horizontal and slit-like and immediately above it is a fold of dura which corresponds with the floor of the lateral sinus. While it is difficult to be certain of the function of this fold of dura, which varies considerably in size from specimen to specimen, it would appear to serve the purpose of directing the blood from the basal vein into the superior occipital sinus. In a previous communication the basal vein has been described as terminating in the lateral sinus; it would perhaps be more correct to describe it as terminating in the superior occipital sinus. It must be admitted, however, that no direct evidence could be obtained of the normal direction of blood flow in the superior occipital sinus and although it seems reasonable to presume that it is downwards towards the inferior occipital sinus it is conceivable that under certain circumstances the flow may be in a reverse direction towards the lateral sinus.

The cavernous sinus receives its blood mainly from the orbit through the ophthalmic veins. Although Ellenberger and Baum describe veins entering the sinus from the cerebral hemispheres, it has been impossible to demonstrate them. The anterior intercavernous sinus is not represented in the dog. The posterior intercavernous sinus, however, is a well-defined structure. The spheno-parietal and the superior petrosal sinuses are also absent in the dog. The petrosal sinus runs backwards from the posterior end of the cavernous sinus in a bony canal, situated between the petrous temporal bone and the basiocciput. The sinus then enters a canal in the substance of the occipital bone where it unites with the superior occipital sinus to form the inferior occipital sinus. A vein passes from the petrosal sinus to the exterior through the foramen lacerum posterius. This vessel is the beginning of the internal jugular vein. The inferior occipital sinus is a very short sinus. It runs backwards and inwards in the interior of the bone and opens on the inner aspect of the condylar portion of the occipital bone. It then passes through the foramen magnum and becomes the vein of the vertebral column. The veins of the vertebral column are large vessels which are continuous throughout the whole vertebral column. In the cervical region they resemble sinuses. They are situated outside the dura, but within the periosteum, and occupy a groove on either side of the posterior longitudinal ligament. They are in frequent communication with each other and receive blood from the spinal medulla and the vertebræ. A vessel also passes to the exterior through each intervertebral foramen. In this way they are brought into communication with the veins of the neck, the intercostal, the lumbar and the sacral veins.

As already stated, the internal jugular vein in the dog is normally a very small vessel. It starts as a small branch from the petrosal sinus which passes through the foramen lacerum posterius. This venule is very soon joined by a somewhat larger vessel from the upper part of the vein of the vertebral column. Occasionally the internal jugular vein is not represented by a single trunk, but by a small plexus of veins which lies along the course of the internal carotid artery.

To summarize, it would appear that blood from the convexity and the greater part of the inner aspect of the cerebral hemispheres and also the bulk of the blood from the interior of the brain find their way to the torcular. After leaving the torcular two routes are available. Blood may leave the cranium through the lateral sinuses and the external jugular veins. This appears to be the normal route. On the other hand, some blood may escape through the superior occipital sinuses and ultimately find its way into the veins of the vertebral column. It would seem probable that the blood from the greater part of the under surface of the cerebral hemispheres and some of the blood from the mid-brain, the pons, and the cerebellum which drain into the basal veins normally leave the cranium through the latter route. Some blood also escapes from the petrosal sinuses into the internal jugular veins.

We are now in a position to consider the effect of experimental obstruction of the venous return of the brain upon the pressure of the cerebrospinal fluid.

I.—THE EFFECT OF OBSTRUCTION OF THE EXTERNAL JUGULAR VEINS UPON THE PRESSURE OF THE CEREBROSPINAL FLUID.

Experimental technique.—Short-haired dogs of the mongrel type which weighed from 7 to 8 kg. were the animals of choice. Reliable results can only be obtained if the animals are strong and in good health. Anæsthesia was first induced by the ether bomb and maintained by intratracheal insufflation. Care is required to maintain the rate of administration as near constant as possible. An abrupt change in the concentration of the ether is followed immediately by changes in the arterial, venous and cerebrospinal fluid pressures. Although an injection of morphia rendered the administration of ether much less difficult, it was found to have a disturbing effect on the pressures which became unsteady, and it was accordingly avoided. Similar observations have been made by Becht [1] and by Weed and Hughson [15]. The animals were maintained in the horizontal position with the head raised slightly above the rest of the body and supported on a block of wood. It was the custom to record a pressure-reading only after it had remained reasonably steady for a period of not less than ten minutes. The cerebrospinal fluid pressure was recorded with a 1 mm. bore straight manometer attached to a needle in a cisterna magna.

The venous pressure at the torcular was recorded in the following way. A quarter-inch trephine hole is made over the superior longitudinal sinus about a quarter of an inch in front of the point where the sinus enters the torcular. The sinus appears as a dark band at the bottom of the trephine hole. The wall of the anterior part of the trephine hole is then trimmed with bone forceps and made to slope. With the aid of a fine needle a small puncture is made into the sinus and a larger short bevelled needle (gauge 18) is then passed through the puncture hole down towards the torcular. This needle is then attached to a 1 mm. bore straight manometer containing a 4 per cent. solution of sodium citrate. Finally the trephine hole is sealed with wax. Care is needed in the choice of the needle for recording the venous pressure. With a small bore needle clotting is liable to occur early, while too large a needle may impede the blood flow through the sinus. Weed and Hughson are of the opinion that obstruction to the flow of blood in the superior longitudinal sinus causes a rise in the pressure of the cerebrospinal fluid and they consider that the absence of such a rise when a needle is introduced into the sinus indicates that there is no obstruction to the blood flow. In none of the experiments which are to be described was a rise in cerebrospinal fluid pressure observed to follow the introduction of the needle. In any case, it is doubtful if the presence of a gauge 18 needle in the posterior end of the superior longitudinal sinus of an 8 kg. dog is likely to cause an obstruction of any consequence. In order to diminish the risk of clotting the following precautions were taken: (1) the needle used for recording the pressure was short bevelled and blunt so as to reduce the risk of injuring the sinus endothelium. (2) Previous to insertion the needle was carefully dried with absolute alcohol and ether and then heated for about ten minutes in liquid paraffin. (3) The manometer contained a 4 per cent. solution of sodium citrate. With careful attention to detail the risk of clotting can be considerably reduced.

Although various degrees of increased intercranial venous pressure can be brought about very conveniently by tying a loop round the animal's neck, this method was found to be unsatisfactory for the purposes of these experiments. It was soon discovered that the swelling of the neck which resulted from this procedure caused the constricting band to exert a gradually increasing pressure on the vessels of the neck. Under these circumstances the venous pressure at the torcular continued to rise as the degree of venous obstruction gradually became more complete. It was decided, therefore, to apply a local constriction to the external jugular veins. In order to achieve this the veins were exposed at the level of the upper part of the trachea and ligatured with catgut. In acute experiments, when it was sometimes necessary to release the vessels rapidly, small clips were placed on the veins. When this method was employed the venous pressure at the torcular reached its maximum almost at once, although it never rose to the heights which were attained when a constricting band was applied to the whole neck.

A record of the arterial pressure was obtained by means of a cannula in the femoral artery. The pressure was not recorded at the common carotid artery as it was considered desirable to avoid as far as possible any interference with the arterial supply of the brain. An experiment was not considered successful unless the systolic blood-pressure remained steady throughout the period of observation. Weed and Hughson [15] state that "Minor slow alterations of the cerebral arterial supply as determined by the carotid pressure seem to have no appreciable effect upon the pressure of either the cerebrospinal fluid or the sagittal sinus tension. Marked sudden alterations in the arterial supply to the structures within the cranial cavity, however, do affect the pressures of the cerebrospinal fluid and superior sagittal sinus—a conclusion held by Dixon and Halliburton and by Becht. This influence of arterial supply, is, however, of apparently less physiological importance than is venous pressure."

In the experiments which are about to be described it was found that minor slow alterations in the arterial blood-pressure had normally little influence upon the cerebrospinal fluid and the torcular venous pressures. When, however, the intracranial venous pressure had been raised by ligation of the external jugular veins the cerebrospinal fluid and the torcular venous pressures were found to be much more sensitive to changes in the arterial blood-pressure. It was necessary, therefore, to have a continuous record of systemic blood-pressure in all experiments dealing with the effect of raised intracranial venous pressure upon the pressure of the cerebrospinal fluid.

(1) *The normal relation of the intracranial venous pressure and the cerebrospinal fluid pressure.*

Table I is a record of the torcular venous pressure, the cerebrospinal fluid pressure and the arterial pressure at the femoral artery in fourteen dogs. The pressures were recorded simultaneously and were obtained during the initial control period of experiments for different purposes. A pressure reading was recorded only when the excursion of the column of fluid in the manometer was of normal amplitude and remained reasonably steady for not less than ten minutes. It will be observed that in these experiments the venous pressure at the torcular never exceeded

TABLE I.—THE RELATION OF THE CEREBROSPINAL FLUID PRESSURE AND THE INTRACRANIAL VENOUS PRESSURE IN FOURTEEN DOGS.

Experiment No.	Cerebrospinal fluid	Torcular venous	Femoral artery
1	95	60	110
2	150	89	115
3	135	65	90
4	130	80	130
5	100	35	120
6	110	50	115
7	125	70	105
8	120	60	95
9	135	110	105
10	90	20	115
11	100	75	125
12	120	65	105
13	110	80	100
14	125	30	135

The cerebrospinal fluid pressure is recorded in millimetres or normal saline solution and the torcular venous pressure in millimetres of 4 per cent. sodium citrate solution.

that of the cerebrospinal fluid. Considerable variation in the height of the venous pressure was observed from animal to animal. In three experiments it was found to be less than 40 mm. of a 4 per cent. solution of sodium citrate. There was no reason to believe that these low readings were the result of errors of technique for in each instance the excursion of the column of fluid in the manometer recording venous pressure was of normal amplitude and the pressure rose and fell normally on temporary compression of the external jugular veins.

(2) *The effect of a temporary occlusion of the external jugular veins.*

Table II is a record of the effect of ligation of the external jugular veins upon the pressure of the cerebrospinal fluid and the venous pressure at the torcular in six dogs. The cerebrospinal fluid pressure and the torcular venous pressure attained their maximum height simultaneously and a few seconds after the veins were occluded. It will be observed that the two pressures may rise to very nearly the same level. In some experiments, however, the level reached by the venous pressure was the higher, while in other experiments the cerebrospinal fluid pressure exceeded the venous. The average proportion of the venous increase of pressure which was reflected in the pressure of the cerebrospinal fluid was 61 per cent. This figure is identical with that obtained by Becht [1]. Occlusion of the external jugular veins was usually found to have no influence on the femoral arterial pressure. Occasionally, however, it was accompanied by a slight but temporary fall of blood-pressure. On release of the jugular veins the cerebrospinal fluid pressure and the

Table II.—The Effect of Temporary Occlusion of the External Jugular Veins upon the Cerebrospinal Fluid and the Torcular Venous Pressures.

Experiment No.	Cerebrospinal fluid	Torcular venous	Femoral artery
1*a*	95	60	110
b	210	195	110
2*a*	150	89	115
b	230	210	115
3*a*	185	65	95
b	255	270	90
4*a*	180	80	180
b	230	280	180
5*a*	100	35	120
b	200	195	120
13*a*	110	80	100
b	190	210	100

a, Pressures before occlusion. *b*, Pressures after occlusion. The cerebrospinal fluid pressure is recorded in millimetres of normal saline solution and the torcular venous pressure in millimetres of 4 per cent. sodium citrate solution.

venous pressure at the torcular returned to their original levels within a few seconds. Not infrequently, however, lower levels were first assumed and then the pressures rose gradually to the original level. These observations are on the whole in harmony with the findings of Becht [1] and of Weed and Hughson [15].

(3) *The effect of prolonged occlusion of the external jugular veins.*

An attempt was now made to determine the effect of a prolonged occlusion of the external jugular veins. In a number of dogs the anæsthesia was maintained for two to three hours and a reading of the pressures was taken at intervals of five minutes. The results of an average experiment are indicated in fig. 2. The cerebrospinal fluid and the torcular venous pressures both begin to fall very soon after they have attained their maximum height. The cerebrospinal fluid pressure at first falls rapidly and then more gradually. The fall often

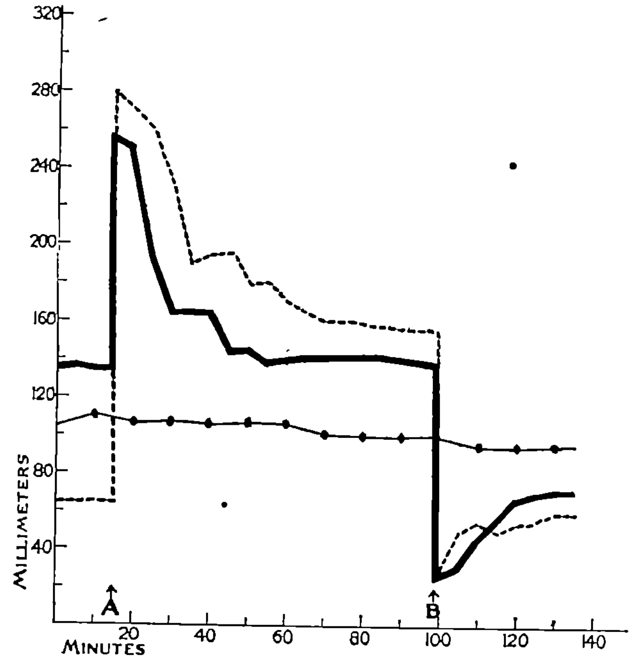

FIG. 2.—The effect of occlusion of the external jugular veins upon the cerebrospinal fluid pressure and the venous pressure at the torcular. The ordinates represent millimetres of normal saline solution or of mercury. The veins were occluded at A and released at B.

Cerebrospinal fluid pressure : ————
Venous pressure at the torcular : - - - - - - -
Systolic pressure at femoral artery : —●—●—

takes place in a step-like manner. A level approximating the original one before the veins were ligatured is usually attained after thirty to forty-five minutes. The pressure then remains steady or continues to fall somewhat below its original level. The fall in the venous pressure is not so rapid or complete. In this experiment it will be observed that by the time the cerebrospinal fluid has attained a pressure which reasonably corresponds to the original one before the veins were ligated, the venous pressure is still nearly three times its original height. In some experiments a much higher venous pressure was found at this point while in others the fall had been more rapid and complete. If the experiments were continued the venous pressure usually became steady, although at a variable height above its original level. It will be observed that in this experiment the cerebrospinal fluid pressure had attained its original level after forty-five minutes, although the venous pressure was not less than three times its original height during almost the whole of this period. The external jugular veins were released one hour and a half after ligation. It will be noticed that the cerebrospinal fluid and the torcular pressures both fell at once to very low levels and that the pressures then rose gradually towards their original levels. On cessation of the experiment thirty-five minutes later, the venous pressure had attained its original level while the cerebrospinal fluid pressure was approximately half its original height.

To summarize, it would appear that the rise in cerebrospinal fluid pressure and in the venous pressure at the torcular which follows ligation of the external jugular veins is of temporary duration. The cerebrospinal fluid pressure has usually returned to its original level after thirty to forty-five minutes. It is noteworthy that this fall often takes place while the venous pressure is several times its original height. The fall in the venous pressure is not so rapid and is often incomplete after several hours. Release of the veins is always followed by a sudden fall of both pressures to very low levels and by a gradual return towards the original level.

II.—THE EFFECT OF OBSTRUCTION OF THE LATERAL SINUSES UPON THE PRESSURE OF THE CEREBROSPINAL FLUID.

Having determined the effect of ligation of the external jugular veins upon the pressure of the cerebrospinal fluid and the venous pressure at the torcular, it was considered desirable to devise if possible some method by which the torcular venous pressure could be raised and maintained at a higher level than that which follows ligation of these vessels. In the hope of achieving this it was decided to occlude the lateral sinuses midway between the torcular and the point at which they are joined by the basal veins (see fig. 1).

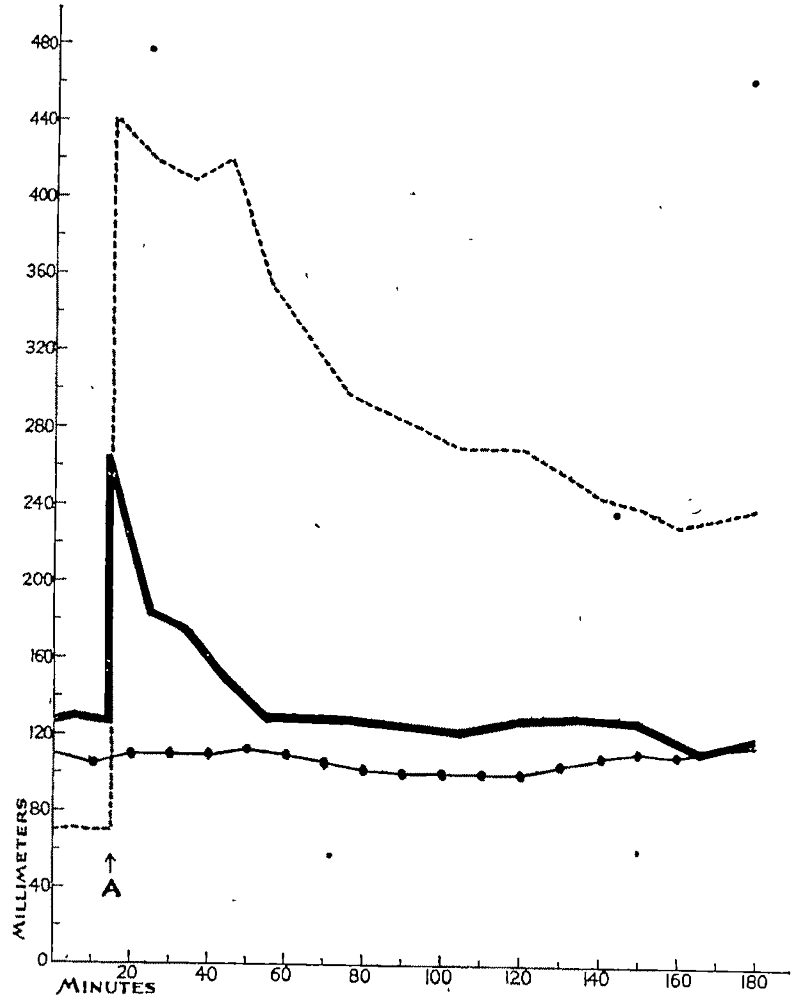

FIG. 3.—The effect of occlusion of the lateral sinuses upon the cerebrospinal fluid pressure and the venous pressure at the torcular. The ordinates represent millimeters of normal saline solution or of mercury. The lateral sinuses were occluded at A.

Cerebrospinal fluid pressure : ———
Venous pressure at the torcular : - - - - - - -
Systolic pressure at femoral artery : —●—●—

Experimental technique.—The bone over the inner third of a lateral sinus was exposed by reflecting part of the temporal muscle. A quarter-inch trephine hole was then made over the lateral sinus about half an inch external to the torcular. The trephine hole was made in such a way that it did not extend below the lower border of the sinus. If this precaution were not taken subtentorial bleeding was very liable to occur. It was desirable, if possible, to expose the sinus without opening it and to occlude it by compressing with wax. By this means, the risk of clotting was greatly reduced. Often, however, the sinus was unavoidably injured by the trephine and it was necessary to occlude it by introducing wax into the lumen. The anterior wall of the lateral sinus in this part of its course is usually ossified and with ordinary care it is easy to avoid compressing the brain with the wax. Obstruction of one sinus alone had little influence on either the venous or the cerebrospinal fluid pressures. On terminating an experiment a careful post-mortem examination was made to verify the position and the extent of the obstructing mass. It was also necessary to determine to what extent clotting had occurred and to exclude the presence of intracranial hæmorrhage.

The results of a fairly typical experiment are illustrated in fig. 3. It will be observed that although the rise in the pressure of the cerebrospinal fluid which follows obstruction of the lateral sinus only slightly is above the level obtained when the external jugular veins are ligatured, the torcular venous pressure rises to a much higher level. In this experiment only 38 per cent. of the venous rise in pressure is reflected in the rise of cerebrospinal fluid pressure. The average finding for six experiments was 42 per cent. This contrasts with the finding after ligation of the external jugular veins when 61 per cent. of the venous rise of pressure was found to be reflected in the cerebrospinal fluid pressure rise. On the whole the general character of the rise and the fall in the pressures resembles that which follows ligation of the external jugular veins. In this experiment the cerebrospinal fluid pressure has returned to a level within 5 mm. of the original level forty minutes after the sinuses have been occluded. At this time the torcular venous pressure is still five times its original height.

To summarize, it would appear that: (1) The pressure changes which follow occlusion of the lateral sinuses bear a general resemblance to those which follow ligation of the external jugular veins; (2) although the rise in pressure of the cerebrospinal fluid is only slightly higher than that which follows ligation of the external jugular veins, the rise in venous pressure is much greater. A smaller percentage of the venous rise of pressure is reflected in that of the cerebrospinal fluid; (3) the cerebrospinal fluid pressure has generally returned to its original level after thirty to forty-five minutes although the venous pressure may still be several times its original height.

DISCUSSION.

It would appear from these experiments that the increase in the cerebrospinal-fluid pressure which follows occlusion of the external jugular veins or of the lateral sinuses of the dog is a temporary phenomenon. When the cerebrospinal-fluid pressure has returned to its original level, the torcular venous pressure is still frequently several times its original height. This is most evident when the lateral sinuses have been obstructed. In these experiments a normal cerebrospinal-fluid pressure was frequently found to be present, while the torcular venous pressure was five or more times its original height. The sudden rise of cerebrospinal-fluid pressure which follows venous obstruction is, as has already been indicated, generally regarded as being due to the direct influence of the raised intracranial venous pressure upon the cerebrospinal-fluid pressure, and is not considered to provide evidence of increased cerebrospinal-fluid formation. The experiments which are now under consideration would appear to indicate that a high torcular venous pressure of several hours' duration is not followed by an increased formation of cerebrospinal fluid. The great vein of Galen is the main route by which blood leaves the choroid plexuses of the lateral and of the third ventricles. The great vein of Galen terminates in the straight sinus, which in turn passes its blood directly into the torcular. Although it is impossible to be certain of the effect of pressure changes at the torcular upon the capillary·pressure of the choroid plexuses, it is probable that they are closely related. These experiments would seem to indicate that the formation of cerebrospinal fluid is uninfluenced by changes in the venous pressure of the Galenic system, and to favour the view that the process is a true secretion rather than a simple filtration. More evidence is necessary, however, before such a conclusion can be accepted. It might also have been expected that the raised intracranial venous pressure would possibly have interfered with the absorption of the cerebrospinal fluid if this phenomenon is normally one of simple filtration through the cerebral villi. It is obvious, however, from a consideration of the anatomy of the intracranial venous system of the dog that in these experiments the degree of congestion must have been most intense in the superior longitudinal sinus and in the Galenic system. The average duration of the experiments was from two to three hours; if, however, it had been possible to continue them for longer periods, it is conceivable that results of a different type might have been obtained.

As regards the cause of the fall in the pressures, it would seem probable that the venous pressure falls mainly on account of the development of collateral circulation, and this is responsible indirectly for part of the fall in the pressure of the cerebrospinal fluid. The occurrence, however, of a normal cerebrospinal-fluid pressure in the presence of a torcular venous pressure which is several times its original height, and also the phenomena observed when the external jugular veins are released after an obstruction of several hours' duration, would seem to suggest that there has been an actual decrease in the total volume of cerebrospinal fluid. The greatest caution must, however, be exercised in attempting to interpret intracranial pressure changes in terms of intracranial volume changes, and until it is possible to employ in these experiments a method capable of recording changes in intracranial volume, the interpretation of these findings must remain mainly speculative.

These experiments do, however, appear to have established that: (1) The rise in cerebrospinal-fluid pressure which follows obstruction of the external jugular veins or of the lateral sinuses is a temporary phenomenon, and (2) an abnormally high torcular venous pressure is compatible with a normal cerebrospinal-fluid pressure.

SUMMARY.

(1) The available literature relating to the influence of increased intracranial venous pressure upon the pressure of the cerebrospinal fluid is reviewed.

(2) The anatomy of the intracranial blood-sinus system of the dog is described.

(3) The effect of a temporary ligation of the external jugular veins and also of a ligation of several hours' duration upon the torcular venous pressure and the cerebrospinal-fluid pressure is investigated.

(4) The effect of occlusion of the lateral sinuses is also investigated.

(5) It is concluded that a torcular venous pressure which has been artificially raised to several times its normal height is not accompanied by any sustained change in the pressure of the cerebrospinal fluid in the course of the next two or three hours.

My thanks are due to Mr. S. L. Prescott for assistance during some of the experiments, and to Dr. N. Shtetinin for the drawing.

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VASODILATATION AND VASOCONSTRICTION IN RESPONSE TO WARMING AND COOLING THE BODY: A STUDY IN PATIENTS WITH HEMIPLEGIA.[1]

BY V. UPRUS (TARTU), J. B. GAYLOR (GLASGOW), D. J. WILLIAMS (MANCHESTER), AND E. ARNOLD CARMICHAEL.

IN a previous paper attention was drawn to the necessity for observing vasoconstriction rather than vasodilatation as an indication of the functional capacity of the sympathetic nervous system. It is the purpose of this paper to describe a series of investigations appertaining to vasoconstriction and vasodilatation carried out on normal people and on patients suffering from the effects of cerebral lesions, and to discuss the interpretation of the results.

METHODS AND MATERIAL.

The method employed to produce dilatation and constriction was that of immersion of the indifferent limbs in tanks of warm and then of cold water. Simultaneous temperature readings were obtained from the cheeks, and the tips of the digits of the hands and feet by means of thermocouples. Rectal temperature was registered by a thermocouple inserted 5 to 6 cm. above the anal sphincter.

Fifteen normal young post-graduates of both sexes, and twenty-two patients suffering from the effects of isolated lesions of the nervous system, were investigated. Many of these investigations were repeated, the technique being modified to elucidate different points.

It is our privilege here to express our gratitude to the members of the honorary medical staff of the National Hospital who so generously permitted us to carry out these investigations upon patients under their care. To the many post-graduates who willingly offered themselves as controls we extend our thanks.

RESULTS.

A. Normals.—A study of the records obtained from the fifteen normal people shows that following immersion of the feet in water at 44° to 45° C. a simultaneous rise occurred in the temperature of the corresponding fingers. Likewise when the arms were immersed in the warm water the rise in temperature of the toes was simultaneous and equally rapid (fig. 1). On immersing one arm or leg, the temperature of the finger rose before that of the toe. The time interval between the two varied from four to seventeen minutes. Irrespective of the limbs under investigation, the rise in temperature of the cheeks always preceded that of the limbs. In every instance no rise in temperature of digits or cheeks occurred before the rise in rectal temperature.

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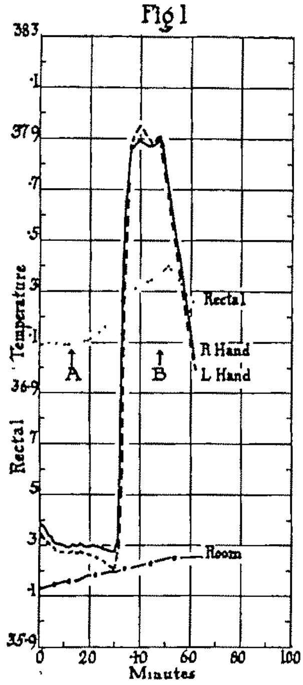
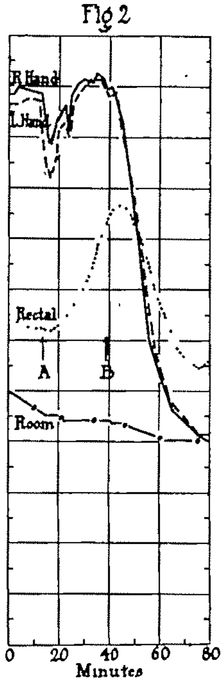
[1] Work undertaken on behalf of the Medical Research Council at the Research Unit, National Hospital, Queen Square, London, while Dr. Uprus held a Rockefeller Foundation Fellowship, and Dr. Gaylor and Dr. Williams Halley-Stewart Research Fellowships.





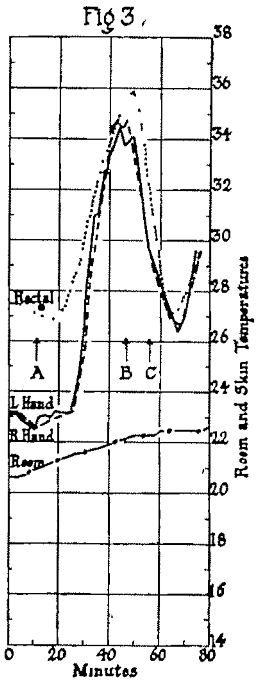


FIG. 1.—A. O., normal. A, feet into water at 45° C.; B, feet into water at 12° C.

FIG. 2.—F., normal. A, feet into water at 45° C.; B, feet into water at 11·5° C.

FIG. 3.—J. L., right hemiplegia. A, feet into water at 44·5° C.; B, feet into water at 11° C.; C, feet into water at 45° C.

In five experiments with different individuals, a fall in the temperature of the digits was observed immediately following the immersion of the legs in hot water. In each, the temperature of the digits was already definitely high. Fig. 2 clearly demonstrates this sequence of events. In only two experiments was a similar fall of temperature of the cheeks observed. The fall in temperature of the fingers was as much as 5° C. in six minutes. A subsequent rapid rise of temperature always took place. This initial fall of temperature was never observed in the feet;

it should be noted that in no case was the temperature of the feet high at the commencement of an experiment.

When the temperature of the digits under examination had reached a nearly stable high level, the indifferent limbs were transferred to tanks of water at 12° to 15° C. Immediately on immersion in cold water, the temperature of the digits of the other limbs began to fall, and in twenty to thirty minutes approximately reached that of the room. Simultaneously with the fall in digital temperature, there was a fall in the temperature of the cheeks. This was not so rapid, nor did it reach so low a level as that of the digits. When thermocouple readings were being taken from the arm and leg, the temperature of the toes fell more rapidly and to a lower level than that of the finger.

Close analysis of the curves of the fall in temperature of the digits showed that for the first minute or two following immersion of the other limbs in cold water, the rate of fall was slow and then rapidly increased. This was more easily observed in the fingers. In two experiments, the initial fall of temperature of the fingers was followed by a slight rise and then a subsequent and more rapid fall of temperature (fig. 2). Synchronous rectal temperature readings demonstrated that the time of onset of this increased gradient or secondary decrease of digital temperature occurred at the same time as the rectal temperature began to fall.

When adequate cooling of the digits had been registered the indifferent limbs were again transferred to warm water. Following this, the rectal temperature continued to fall for several minutes and then began to rise. After the rectal temperature had begun to rise the temperature of the cheeks and then that of the digits rose rapidly. In every way the curve of the skin temperature was similar to that following the earlier immersion in hot water. It differed, however, in its relationship to actual rectal temperature. In every instance the rise in the digital temperature occurred when the rectal temperature was at a lower level than on the first occasion.

These experiments show that in a normal individual the rise in the temperature of the digits of similar limbs is synchronous when the method of immersion is used. Again, it has been shown that the face warms first, then the hand, and lastly the foot. The rise in temperature of the digits only occurs after the rectal temperature has risen, but it is not dependent upon the actual rectal temperature. Following cooling, like digits of two limbs show a similar and synchronous fall of temperature.

HEMIPLEGIA.

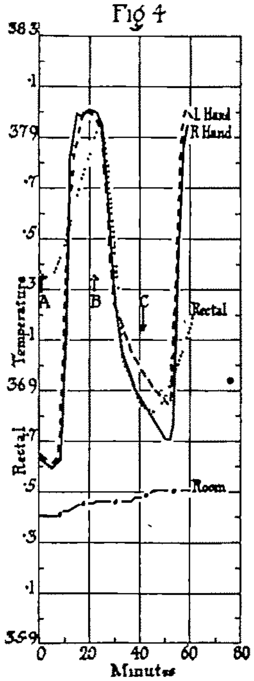
A series of twenty-two patients with evidence of involvement of either the motor or sensory functions of one hemisphere were investigated. Of these twenty-two cases, thirteen had vascular lesions and nine tumour growths. The age of the lesion was from 6 days to 10½ years. Cases with lesions situated in each lobe of the hemisphere were examined. Further, patients with cortical and deep lesions were studied. The degrees of dysfunction varied from slight disturbance to an apparently complete loss of function. For instance, the motor defect varied from slight to practically complete loss of voluntary movement; sensory disturbance was minimal in some, and very considerable in others. Many cases were examined on more than one occasion, and patients with cerebral tumour were frequently tested before and after operation.

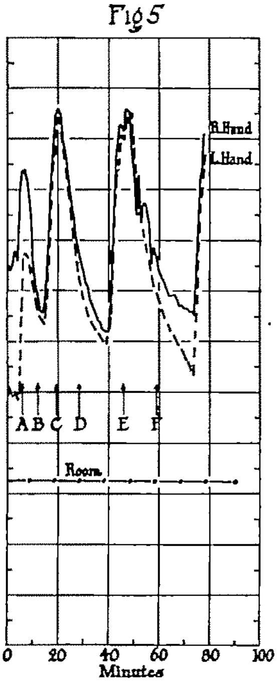
It was found in this series of cases and on repeated investigations on the same patient that there was no constancy in the temperature differences of the two sides. In several cases with cerebral lesions, the affected side was higher in temperature one day, to be lower than the normal on the next.

Following immersion of the indifferent limbs in tanks of warm water, the temperature of the digits of the two arms or two legs rose simultaneously, and equally rapidly, to reach a maximum in a few minutes. In no case was any delay encountered in the affected limb, nor did the rise of temperature of that limb precede that of the normal. In all cases the rise of temperature of the digits followed the rise in temperature of the rectum (fig. 3).

After adequate warming of the digits had occurred, the indifferent limbs were placed in cold water. Following this procedure the observations made were similar in every way to those in the series of normals. If records were obtained from the fingers, those of both hands cooled equally rapidly (fig. 3). Three exceptions were found to this. In these, compared with those of the normal side, the digits of the affected hand cooled less rapidly, and in a more irregular manner (fig. 4). Observation showed that in each of these cases the affected limb was spastic, and that during the time of cooling there was adduction of the arm with flexion of the fingers and wrist. The irregularity of the fall in the digital temperature on the affected side took place when the limb was moved. In such cases the digits of the lower limb showed a fall in temperature which was equal and regular on the two sides. No alteration in posture of the lower limbs took place during the cooling.

A low temperature of the digits having been produced, the limbs immersed in the cold water were transferred to water at 44° to 45° C. Following this, after the rectal temperature had begun to rise, the temperature of the digits again rose—that of the fingers and toes of each side together.





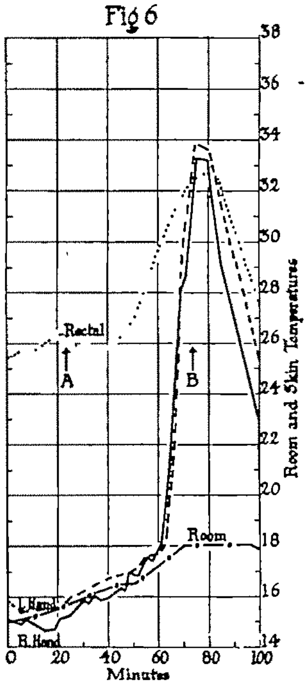


FIG. 4.—E. S., left hemiplegia. A, feet into water at 44·8° C.; B, feet into water at 12·5° C.; C, feet into water at 44·5° C.

FIG. 5.—A. C., normal. A, feet into water at 43° C.; B, water heated to 45° C.; C, feet into water at 10° C.; D, feet into water at 45·5° C.; E, feet into water at 12° C.; F, feet into water at 45° C. Until the forty-fifth minute the arms and hands were in similar positions. After that the right hand was held in a hemiplegic posture.

FIG. 6.—McK., paraplegia. A, legs into water at 44° C.; B, legs into water at 18° C.

These experiments demonstrate that, in the presence of lesions of the cerebral hemispheres, irrespective of site, in response to changes in blood temperature, the rise and fall of temperature of the digits of the two hands, or of the two feet, are synchronous and of similar rate. The only exceptions are in those cases with marked spasticity of the arm when the temperature of the fingers of the spastic arm falls irregularly.

The following experiment was undertaken to investigate this later phenomenon. As the observations suggested that the spastic alteration in posture produced this irregularity of fall of temperature, it was decided that a healthy subject should imitate the abnormal posture and movements. Fig. 5 shows the result obtained. During the first period of cooling the arms were comfortably supported at the side as in the previous experiments. Following the subsequent warming, cooling was again induced, and during this period of cooling the right arm was voluntarily placed in the hemiplegic posture. In this instance cooling was less rapid and more irregular than in the left finger, which was kept supported at the side. The final temperature of the right finger was warmer than that of the left. This procedure was carried out in three normal individuals and gave results similar to those portrayed in fig. 5.

DISCUSSION.

These observations have shown that, with certain minor differences, a rise and fall of skin temperature, similar to that seen in the normal, occurs in response to warming and cooling the body in patients suffering from hemiplegia. At the commencement of an experiment, the hemiplegic limb was sometimes colder or even warmer than the normal limb. This variation in the temperatures of corresponding skin areas on both sides of the body bore no demonstrable relationship to the site or age of the cerebral lesion. However, there may be an apparent delay in cooling of the hemiplegic limb. This may be taken as indicative of dysfunction of the sympathetic system. Before accepting such an hypothesis, it is well to take other factors into consideration.

It has been shown in these investigations that, during the period of cooling, the spastic hemiplegic limb tends to adduct at the shoulder and to flex at the wrist and finger-joints when the motor involvement is severe. As a result of this movement the fingers are brought closer together and nearer to the body. The closing of the fingers causes the approximation of comparatively warm surfaces, and prevents free cooling of these surfaces. In this way loss of heat, as indicated by a fall of temperature readings of the digits of the hemiplegic limb, may appear more slowly than in the opposite and healthy limb. Since a fall in skin temperature readings is indicative not only of a diminished blood flow, but also of the capacity of the limb to cool, it is essential to take into account the facilities for cooling. That the posture adopted in these cases during the cooling is of importance is evidenced by the experiment in which a normal individual was subjected to cooling on two occasions. Here it was found that when the limbs were kept in a similar position, cooling was equally rapid on the two sides; but when one limb adopted the hemiplegic posture, cooling was less rapid on that side. This evidence strongly suggests that the posture, quite apart from the site of the lesion producing the posture, may account for the lack of synchronous cooling in the two limbs of a hemiplegic patient.

When describing the investigations undertaken, attention was drawn to the immediate cooling of already warm limbs on placing the indifferent limbs in warm water. As the water was of a temperature of 44° to 45° C. the sensation when immersing the limbs was at first unpleasant if not actually painful. It is, therefore, probable that this unpleasant sensation produced a vasoconstrictor response which showed itself by a cooling of the limb under investigation. Again, it was observed that in one or two subjects the immersion of the feet in cold water was followed by an immediate but short-lived cooling of the hands, with a subsequent warming and then a very marked cooling. The second cooling synchronized with the fall in rectal temperature. The immediate cooling was the result of constriction produced by the sensory stimulus of cold. This sensory stimulus was not sufficient to keep the vessels constricted, and they again dilated, only to constrict when the blood temperature, as indicated by the rectal temperature, began to fall. That such an explanation is likely to be true was demonstrated by a study of what occurs in the hands of a patient with a complete paraplegia when the lower limbs are used for immersion. In such a case cooling of the upper limbs did not occur till the rectal temperature had begun to fall (fig. 6). Thus it may be deduced that on immersing the limbs in cold water, two mechanisms play a part in bringing about the cooling of the upper limbs, first a sensory stimulus producing vasoconstriction, and secondly a vasoconstriction dependent upon the fall of temperature of the blood. A study of the results obtained from patients with hemiplegia shows clearly that both mechanisms act in the hemiplegic as in the normal limb.

The work described in this paper therefore favours the view that lesions of the cerebral hemispheres do not in any way alter the functional capacity of the blood-vessels of the hemiplegic limb to constrict in response to a sensory stimulus or to a fall in blood temperature; and secondly that, provided an adequate warming stimulus is presented, the blood-vessels of the hemiplegic limb will dilate as in the normal limb.

SUMMARY AND CONCLUSIONS.

Constriction and dilatation of blood-vessels in response to cooling and warming the body occur in the hemiplegic limb as in the normal limb.

Any delay in cooling the hemiplegic limb is the result of poor facilities for cooling owing to approximation of warm surfaces brought about by posture.

Vasodilatation and vasoconstriction of the vessels of the limbs in response to warming and cooling the body are not affected in degree or in time of onset by lesions of the cerebral hemispheres.

VASOMOTOR RESPONSES IN HEMIPLEGIC PATIENTS.[1]

BY G. STÜRUP (COPENHAGEN), B. BOLTON (LONDON), D. J. WILLIAMS (MANCHESTER), E. ARNOLD CARMICHAEL.

THE investigation of the responses of the sympathetic nervous system of man to various stimuli offers a method of analysis of the functional activity of this system in both health and disease. Of the different manifestations of sympathetic activity the vasomotor response provides a readily demonstrable and efficient indication of the state of the sympathetic system. Accordingly the vasomotor responses of normal subjects and of patients with diverse cerebral lesions have been investigated in some detail and an attempt has been made to record these changes accurately.

Skin temperature readings with thermocouples, as an indication of vasomotor activity, are subject to many uncontrollable variables. The posture of a limb, the local facilities for cooling, the condition of the skin, the activity of the sudomotor system, and the external temperature, each play a determining part in such temperature readings. It has been deemed advisable therefore to evolve a more exact method of registering vasomotor activity. A recognized method of undertaking such a study has been by plethysmography, and the literature on the subject is immense. In the earlier recorded investigations plethysmographic records of a whole limb were obtained by means of the Lehmann [2, 3], or a similar plethysmograph. As muscles are included within this apparatus it is impossible to deduce that the volume changes observed are entirely the result of change in blood volume and are not in part the result of changes in muscle state. Other investigators have constructed smaller plethysmographs; Weber [6] used an ear plethysmograph, and Lombard and Pillsbury [4] a finger plethysmograph. Unfortunately the latter apparatus was too delicate to use in a study of clinical material, and did not permit of more than one digit being examined at a given time. Moreover it was found that a single subject varied in the character of the responses and it was therefore suggested that this variability depended upon the degree of "spasm" of the sympathetic nervous system. Cognizant of these difficulties and criticisms, an attempt has been made to evolve a satisfactory method of investigating the activity of the sympathetic vasomotor fibres of man in health and disease. It is the purpose of this paper to describe the method used, to record the results obtained in normal subjects and in patients with cerebral lesions, and to discuss their interpretation.

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[1] Work undertaken on behalf of the Medical Research Council at the Research Unit, National Hospital, Queen Square, London, while Dr. Sturup held a Rockefeller Foundation Fellowship and Dr. Williams a Halley-Stewart Research Fellowship.

METHOD.

This has been described in detail in another paper [1]. Briefly, a digit was inserted in a glass container moulded to the shape of the finger or toe. Proximally the container was sealed round the finger with zinc oxide paste, and distally it was connected by means of pressure tubing to a thistle funnel covered with a rubber diaphragm, attached to which was a mirror. By means of a beam of light reflected from this mirror on to a moving strip of bromide paper, a continuous record of the changes of volume of a digit was obtained. By erecting a battery of diaphragm recorders, each connected to a different digit, it was possible to obtain synchronous records of changes of volume from several digits of one limb, or from individual digits of two or more limbs. As the rate of recording adopted was slow, the instrumental latent period of less than one-tenth of a second was negligible.

In order to ascertain if there was a quantitative difference in the bilateral response, a modification was introduced into the apparatus as originally described. The diaphragm recorders of two similar digits were repeatedly switched over in order that the possible errors caused by differences in the volume of air in the systems and in the tension of the tambours might be eradicated. In order to equalize the pressures in the system a water manometer was introduced, and the systems equilibrated before each set of stimulations was applied.

The subject was warmed by the immersion of one or two limbs in tanks of water at 44° to 45° C. in order to obtain a steady base-line from which to elicit responses. During this period of warming a continuous record of the changes of digital volume was obtained. It has been shown previously that this method of warming produces a widespread vasodilatation. During this state of dilatation a series of stimuli were given and records taken. The subject was then cooled down by placing the indifferent limbs in cold water at 10° to 12° C. Continuous records were obtained during this phase of the investigation. Skin temperature readings were taken by thermocouples from the tips of the fingers and toes throughout the experiment, and alterations in rectal temperature were registered every quarter of a minute by a thermocouple placed 5 to 6 cm. above the anal sphincter. During the initial control period, and after the subject had been cooled down by immersion of the indifferent limbs in cold water, a similar series of stimuli was repeated.

The stimuli used to provoke vasomotor responses were various. These stimuli may be classified conveniently as extrinsic—cold, pressure, pain, noise; intrinsic—deep breathing, altered blood temperature, visceral pain; mental activity—calculation, word association. Other stimuli such as the threat of injury were also used. Each stimulus was known to be of sufficient intensity to produce a response in normal people. In every experiment a record of the phases of respiration was made by attaching a balloon to the chest. This was necessary in order to determine that the vasomotor response following the known stimulus was not the result of an alteration of respiratory rhythm. During the experiment the subject had his eyes closed and silence was demanded in the experimental room.

It is a pleasure to record our thanks to the members of the honorary staff of the National Hospital who kindly allowed us to carry out investigations upon patients under their care. To the post-graduate students who offered themselves as controls we also express our gratitude.

RESULTS.

In a study of normal people it was found that if the subject were kept in a warm state by immersing one or more limbs in a tank of water at 45° C., the volume of a digit kept nearly constant (fig. 1). Two to three seconds following an extrinsic stimulus, such as a noise or pinch, there took place a diminution in the volume of the digits under investigation (fig. 1). This change of volume took place synchronously in all four limbs and reached its maximum in six to twelve seconds; the volume then returned over a period of a minute to its previous level.

Before investigating normal or abnormal cases it was established by the following series of experiments that the diminution in digital volume was in fact the result of a nervous vasoconstriction. In one patient, who had the right brachial plexus torn across eighteen months previously, and in whom there was wasting of the muscles of that limb and a complete anæsthesia, tests were carried out by taking observations from the fingers of both hands. Following a pinch in a sensitive area no diminution in the volume of the digits of the limb with the ruptured brachial plexus took place; in the digits of the other limbs it did occur (fig. 2). This demonstrated that the diminution of digital volume was dependent upon the integrity of the peripheral nervous system.

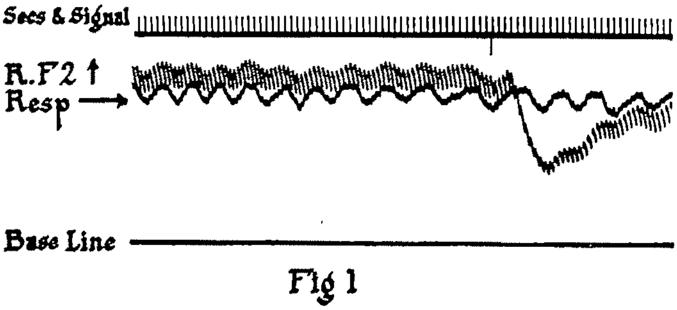

FIG. 1.—Normal. During a period of one minute there is no variation of volume of the finger apart from changes associated with normal respiration. At a signal a shout was given with resultant marked diminution in volume of the digit. The letters to the left indicate the digits. RF2 refers to 2nd right finger. In this and subsequent figures the RT or LT refers to right or left toe. The arrow following the identification mark of the digits points in the direction of an increase in volume. The downstroke in the respiratory tracing is the inspiratory phase. All records read from left to right.

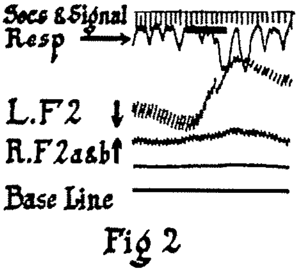

FIG. 2.—Lesion of right brachial plexus. Pinch left arm.

In two subjects, in whom a unilateral stellate ganglionectomy had been performed, no diminution in volume in the digits of the sympathectomized limb occurred following a stimulus. In another patient, who had had a unilateral lumbar ganglionectomy, there was no change in volume of the toes of that side following a pinch (fig. 3). These experiments established that the diminution in digital volume was dependent upon the integrity of the post-ganglionic sympathetic nerve-fibres. They also established that the recorded changes were not the result of movement of the digit within the container.

In a patient with a compression lesion of the cauda equina following an accident and in whom, at operation, the roots of the cauda equina were found to be grey, diminution in volume of the toes of both feet took place at the same time as that in the digits of the upper limb (fig. 4). In this patient the level of anæsthesia indicated that there was no disturbance of the function of the lower dorsal and first lumbar roots by which the vasomotor preganglionic fibres to the leg leave the cord. But there appeared to be complete interruption of the lower lumbar and sacral anterior and posterior roots. It was therefore evident that the diminution in volume of the toes was independent of the motor and sensory nerves, and was accounted for by the integrity of the preganglionic fibres in the lower dorsal and first lumbar roots.

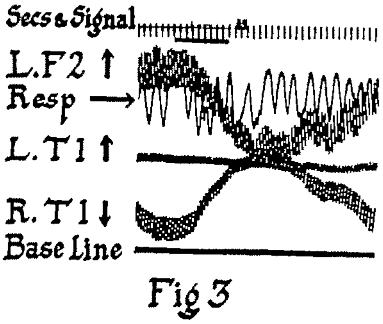

FIG. 3.—Left lumbar sympathetic ganglion excised. Pinch right arm.

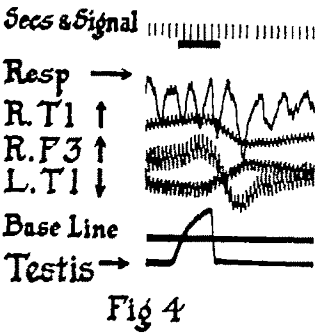

FIG. 4.—Lesion of cauda equina. Pressure of testis.

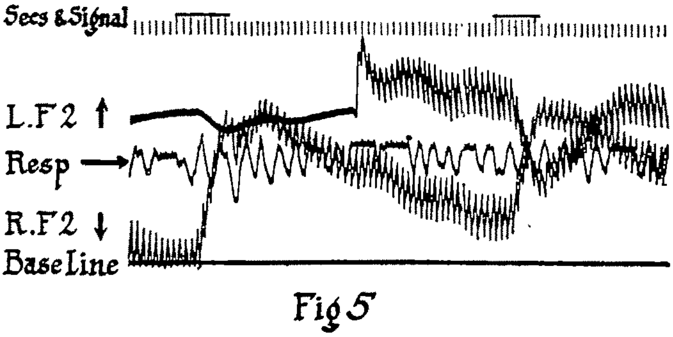

FIG. 5.—Normal. Circulation occluded in left arm during first period, then released. Pinch on right leg during and after occlusion of the circulation.

In three normal people the circulation in one limb was suddenly occluded by rapidly raising the pressure in two sphygmomanometer cuffs, placed respectively on the forearm and upper arm, to over 200 mm. of mercury. Any stimulus sufficient to produce a diminution in volume of the digits with normal blood supply caused a synchronous change of the finger to which the circulation had been occluded (fig. 5). The diminution in volume of a digit was therefore not the result of alteration of heart output or of venous pressure.

These experiments showed that the alteration in volume of a digit, following an extrinsic stimulus, was dependent upon the integrity of the sympathetic nervous system. As the digits contain no muscle tissue this alteration in volume of a digit is therefore only explicable by an active vasoconstriction.

A study was made of twelve post-graduate students attending the hospital. None had evidence of vascular disease of the extremities. In the dilated state and irrespective of the nature of the stimulus a diminution in volume of the digits of the four limbs occurred synchronously after the commencement of any given stimulus. A painful stimulus, e.g. a pinch, or pin-prick, either single or multiple, caused a response wherever the site of stimulation. A sudden noise, such as was made by dropping a plank on the floor or shouting, was followed by a diminution in digital volume. Visceral pain, caused by pressure on the testicle, produced a similar response. The application of ice to any part of the exposed body was an adequate stimulus. Deep inspiration also resulted in a peripheral vasoconstriction [1].

If the subject were given some mental exercise, such as the multiplication of two figures, a diminution in volume of the digits took place in all four limbs. Again, word association resulted in a diminution in volume. The threat of injury, for example the threat of a blow on the face, was followed by a similar alteration in volume. All forms of stimuli resulted in synchronous vasoconstriction of the peripheral blood-vessels of the four limbs. The fall in finger volume did not immediately follow the stimulus. In every case there was a latent period which was never found to be less than one and a half seconds or more than three and a half seconds. It was the rule to find a sharp diminution in finger volume two and a half to three seconds after the stimulus was applied. When the stimulus was instantaneous and could be recorded with a fair degree of accuracy, such as a sudden loud noise or sharp pin-prick, the latent period was remarkably constant, being within two and a half to three seconds. With an intrinsic stimulus, such as a deep breath, it was impossible to ascertain the latent period, as it was not known at what time the stimulus, i.e. the degree of inspiration, had become adequate. Even here, however, the change in finger volume occurred within four seconds of the commencement of deep inspiration.

During the course of these experiments with extrinsic stimuli several interesting observations were made. For instance, when forceps were laid on the skin without an actual pinch being made, a diminution in volume of the digits occurred. Upon holding the forceps there, and then giving a series of pinches at a time interval of thirty to forty-five seconds, diminution in volume occurred with the first pinch; but with succeeding pinches this gradually grew less, eventually ceasing to occur after the fourth or fifth stimulus. This was observed even though the last caused as much pain as the initial stimulus. If at this stage another stimulus, either of the same character or otherwise, were given at another site, widespread and well-marked diminution in digital volume resulted. When a pinch or multiple pin-pricks were continued for a period of a minute, during which time the subject continued to feel pain, a diminution in volume occurred at the commencement; gradually the volume returned to its original level (fig. 6).

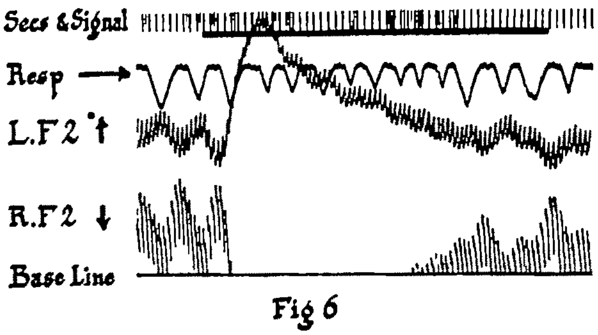

FIG. 6.—Normal. Pinch continued over a period of one minute. The arrows following L.F.2 and R.F.2 should point in the opposite direction.

Finally, it has been shown that the diminution in finger volume occurred irrespective of the respiratory rhythm. This was shown in two ways. First, the various stimuli were unassociated with an alteration in the respiratory rhythm (fig. 6). Secondly, with the breath held, a stimulus, such as a pinch, caused a diminution in volume of the digit, which returned to its preceding level during the period of holding of the breath (fig. 7).

With the subject in an initial state of vasoconstriction, further vasoconstriction as a result of a stimulus was difficult to demonstrate. Conversely, in the presence of vasoconstriction, vasodilatation would be more evident. Although further vasoconstriction could still be produced, no vasodilatation ever occurred following a stimulus. During the period of increase in rectal temperature following the immersion of the indifferent limbs in warm water, an increase in digital volume was observed. This dilatation commenced only after the rectal temperature had begun to rise. Concurrently with the increase of finger volume there was an increase in the amplitude of the pulse wave. Fig. 8 shows clearly that this change is coincident with changes in the degree of vasodilatation. Irrespective of the limb used for immersion, the corresponding digits of the other limbs dilated synchronously in every case. When digital temperature readings were being recorded simultaneously, the dilatation preceded the increase in skin temperature.

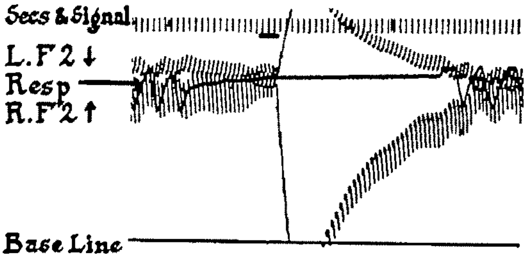

Fig 7

FIG. 7—Normal. Pinch during a period of voluntary apnœa.

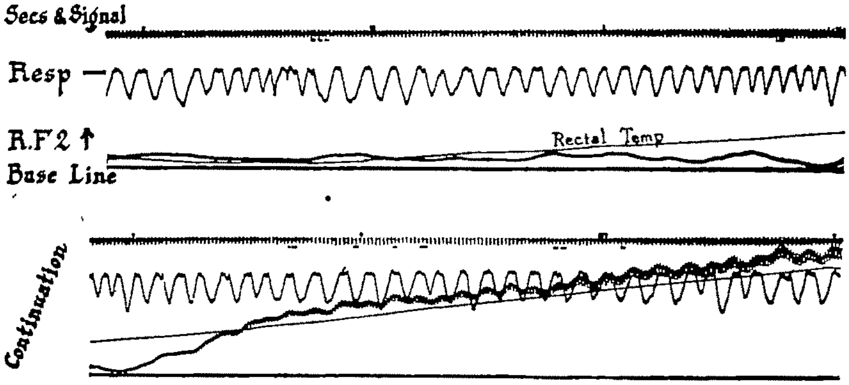

Fig 8

FIG. 8.—Normal. Period of warming up. Record of change in rectal temperature and in volume of right finger.

On transferring the indifferent limbs to water at 10° to 12° C. there was an immediate constriction followed by a slow dilatation. This lasted for one to two minutes and was then replaced by a progressive vasoconstriction. This later vasoconstriction succeeded the fall in rectal temperature by a short time interval (fig. 9).

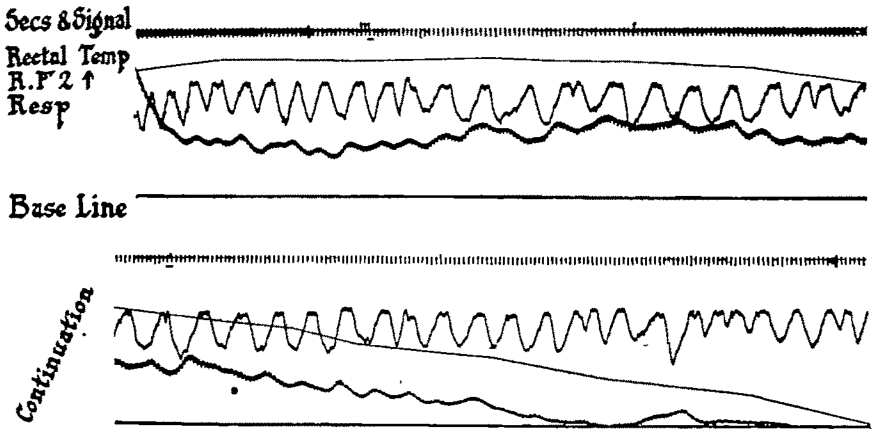

Fig 9

FIG. 9.—Normal. Record of commencement of cooling. At the beginning of the record the indifferent limbs were placed in cold water. The immediate diminution in volume is seen followed by an increase of volume of the digit. The curve of rectal temperature is plotted.

HEMIPLEGIA.

In all twenty-three patients with lesions of the cerebral hemispheres were examined. Of these, nine had symptoms of severe motor involvement, five of sensory involvement, four of both. Three had lesions of the frontal lobe, one a lesion of the occipital pole, and another of the temporal lobe. Fig. 10 illustrates the site of the lesion in these cases. Eleven patients were suffering from cerebral tumour, and ten from a vascular lesion. Cortical atrophy was the cause of the symptoms and signs in one patient and trauma in another. The age of the lesion varied from six days to twenty years. Several of those subjects suffering from cerebral tumour were examined before and after operation. Care was taken to exclude all patients who had gross evidence of vascular disease of the peripheral blood-vessels. Only patients in whom an accurate clinical localization of the lesion in the cerebrum was possible were included in the series, and the diagnosis of a few was subsequently confirmed at autopsy.

In all cases symmetrical synchronous records were obtained. In the majority corresponding fingers were used, in others corresponding toes. Records were taken from digits of three and even four limbs simultaneously in several cases. In the latter instance the subject was warmed by several hot-water bottles and extra blankets. Though not so efficient as the immersion method for giving a steady baseline, it was still possible to determine the presence or absence of diminution of digital volume following appropriate stimuli.

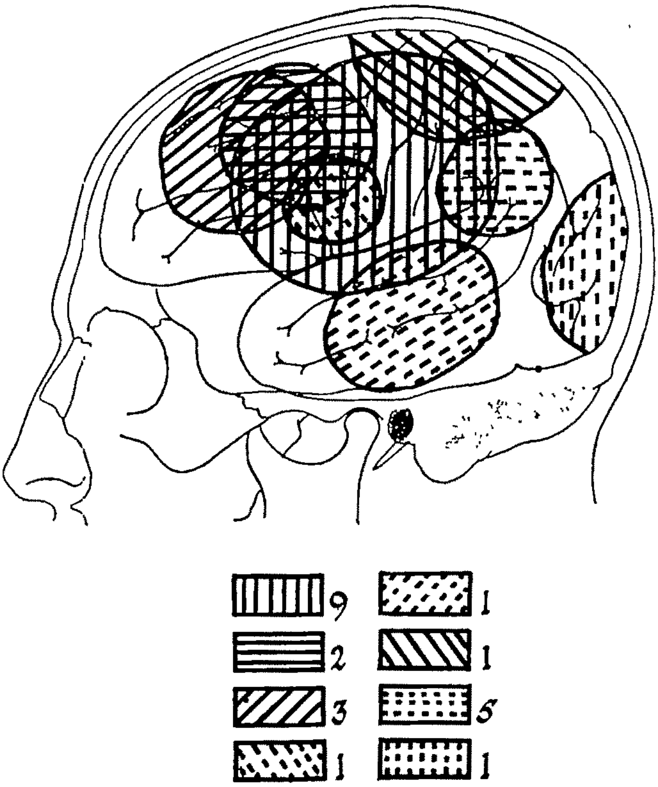

FIG. 10.—Chart of sites of cerebral lesions.

The results of these observations may be quite briefly given: for no matter where the site of the lesion in the hemisphere, or what the degree of dysfunction of motor, sensory, or of reflex activity, the results so obtained were identical with those from normal individuals. In those subjects with marked sensory disturbance on the one side, extrinsic stimuli applied to the affected side caused a similar response to that produced by stimulating the normal side. Further, in subjects with severe motor involvement or in those suffering from a lesion of the frontal lobe, the diminution in volume of the digits of both upper limbs was alike in response to the stimuli. Mental activity, fright and visceral pain also produced symmetrically good responses. The outcome of these investigations was to demonstrate that with lesions of the cerebral hemisphere, no matter the site or the resultant severity of dysfunction, vasoconstriction could be produced in the fingers or toes of the two sides with ease and regularity equal to that in normal individuals (figs. 11, 12, 13).

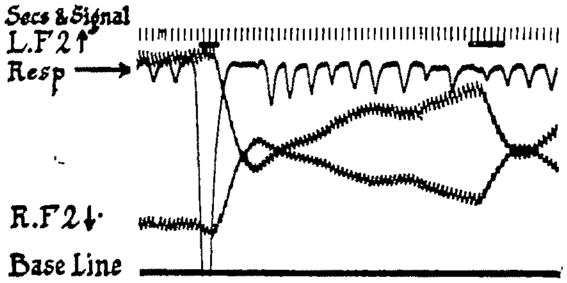

Fig 11

FIG. 11.—Left frontal lobectomy. Deep breath and pinch of right arm.

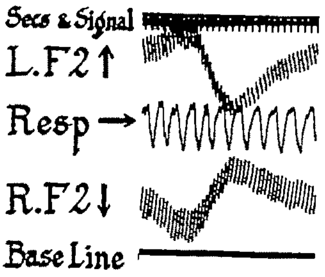

Fig 12

FIG. 12.—Left motor cortex destroyed. Shout.

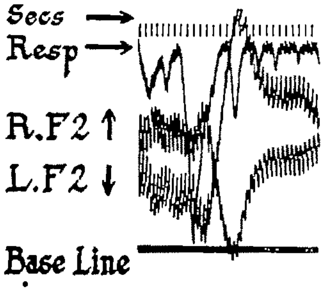

Fig 13

FIG. 13.—Left parietal lobe lesion. Deep breath.

In twenty patients tests were carried out with the subject in a cool state—namely one in which vasoconstriction of the peripheral vessels was present. The presence of vasoconstriction was assumed by the temperature of the fingers, measured by thermocouples, and also by plethysmographic records which illustrated the relative smallness of the pulse-wave in the records. During this state of vasoconstriction they were subjected to all the stimuli which have been described. A close analysis of the records failed to demonstrate any response which could be interpreted as indicative of dilatation.

Twenty subjects with a lesion of one hemisphere, who were in a cold state, were warmed up by placing either the legs or arms in tanks of water at 44° to 45° C. During this period continuous records were taken from the digits of the other limbs. After an irregular period of time, varying from three to fifteen minutes following immersion, and only after the rectal temperature had begun to rise, an increase of volume of the digits occurred, associated with an increase in the amplitude of the pulse-waves. The records showed that the increase in volume and pulse-wave amplitude occurred synchronously in the digits of both arms or legs. No priority or delay was ever seen in the dilatation of the hemiplegic limb.

Lastly, after taking records while in a fully dilated state, the subjects were cooled rapidly by transferring the indifferent limbs from tanks of warm water to tanks of water at 12° to 15° C. Immediately upon placing the limbs in the cold water a diminution in volume of the digits under observation took place; this was followed by a slow dilatation but not to the level attained before cold immersion. This period of slow dilatation was followed one to two minutes later by a renewed diminution in volume and lessening of the amplitude of pulse-wave. Synchronous rectal temperature readings showed that the secondary diminution in volume occurred at the same time as the rectal temperature ceased to rise and began to fall. The records obtained from patients suffering from cerebral lesions demonstrated that, on immersion of the other limbs in cold water, the vessels of the digits of both the hemiplegic and normal limb constricted, then dilated and finally constricted synchronously. No record was obtained which showed any delay in the healthy or hemiplegic limb.

DISCUSSION.

In these experiments care was taken to exclude movement of the recording digits and to ensure complete absence of congestion of the digit by pressure of the proximal end of the plethysmograph. These variables being absent, change in the volume of the finger could only be brought about by change in heart output, venous pressure, or by active alterations in the state of the vascular network of the digit. After completely occluding the circulation of an arm by a sphygmomanometer pressure of 200 mm. Hg it has been shown that a diminution occurred in the volume of the finger after stimulation. The curve of this diminution of volume was of the same type and had the same time relations as those changes produced in the presence of a free circulation. It can therefore be affirmed that these changes in the digital volume are directly produced by changes in the vascular bed—that is, by vasoconstriction. Experiments on patients with lesions in different sections of the peripheral pathways have been described. It has been shown that vasoconstriction in response to intrinsic and extrinsic stimuli is independent of the integrity of the anterior and posterior roots of the recording limb, but that it is dependent on the continuity of both the pre- and post-ganglionic sympathetic nerve-fibres. It is therefore a mechanism whose efferent pathway is a sympathetic nerve-fibre. In the patient with the cauda equina lesion, although stimulation of the skin above the level of anæsthesia caused a vasoconstriction in the affected limbs, stimulation of the anæsthetic limbs did not produce vasoconstriction. Again in the patient with the brachial plexus injury, stimulation of the affected limb caused no constriction in other limbs. In the sympathectomized patient however, stimulation of the periphery of the sympathectomized limb, although causing no change in volume of the sympathectomized fingers, resulted in vasoconstriction in the normal digits of the other limbs. This evidence points to the necessity of an intact sensory pathway when stimuli such as pain, cold, pressure were used.

The latent period of the vasoconstrictor response has been described above. The intensity and the type of stimulus applied did not appear to bear any relation to the latent period observed, although they did affect the degree of vasoconstriction. The constriction was synchronous in all the digits examined.

It has been said that the subjects were examined in dilated and in constricted states. In the course of the experiments stimuli of all the types described above have been applied repeatedly in different ways, but when a response has been elicited it has invariably been a vasoconstriction.

The regional distribution of the lesions has been described. Reference to fig. 10 shows that several regions are represented by more than one patient and it is our belief that the extent of damage illustrated is not excessive. It is therefore unlikely that any part of the motor or sensory areas can have escaped damage in this series. The age of these lesions and the degree of motor and sensory involvement has also been ascertained. In the presence of such damage, with resulting dysfunction, no difference from the normal in the vasomotor responses were found in these subjects. Both the time relationships and degree of vasoconstriction were unchanged. As has been pointed out above, the vasodilatation and vasoconstriction in response to alterations in blood temperature were identical in the normal and hemiplegic side.

In a paper [5] dealing with skin temperature readings it has been shown that in hemiplegia no consistent difference in the initial skin temperature could be found between the two sides. The alteration in skin temperatures in response to changes in blood temperature was similar. It was shown further that the skin temperature of the hemiplegic side might be influenced by posture and bore no relation to the age of the lesion. These conclusions are confirmed by the results of the present paper. It can be affirmed that these investigations provide evidence that, in the presence of lesions of the cerebral hemisphere, the vasomotor control of the limbs is unaffected.

CONCLUSION.

No abnormality of the vasomotor responses in the limbs has been found in the presence of lesions of the human cerebral hemisphere.

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MYOGRAPHIC AND ELECTROMYOGRAPHIC STUDIES OF MYASTHENIA GRAVIS.[1]

BY DONALD B. LINDSLEY.[2]

MYASTHENIA gravis is a condition characterized by marked muscular weakness and excessive fatiguability, particularly in the muscles innervated by the cranial nerves. In such cases chewing, swallowing, keeping the eyes open, holding the head erect and speaking are difficult. The weakness and fatiguability often extend to the muscles of the limbs and trunk so that the patient not only experiences difficulty in breathing, but also in maintaining his general welfare.

Little is known about the cause or exact nature of this disorder. No consistent and definite pathology of either the peripheral or central nervous system has been demonstrated. Minor anatomical changes occasionally found in the muscles are probably not of primary significance. During the past few years, reports by Boothby [1], Remen [2] and others on the beneficial results of glycine treatment have pointed to a disturbance of creatine and creatinine metabolism in myasthenia gravis. Nevin [3], however, in a recent study of the phosphorus-holding compounds of muscle in myasthenia gravis, found them normal and concluded that there is no abnormality in the intrinsic chemical mechanism of muscular contraction in this disorder. He believes that alterations in creatine metabolism are secondary effects of the disease. Simon [4] has recently reported marked improvement in two cases of myasthenia gravis following treatment with anterior pituitary extract.

The view that the transmission of excitation is somehow impaired in the region of the "myoneural junction" has arisen partly because of the exclusion of other factors, and partly because of Edgeworth's [5, 6] discovery that ephedrine is of value in the treatment of this disorder. Recent success in temporarily relieving myasthenic symptoms with physostigmine [7, 8] and the synthetic drug, Prostigmin [9, 10, 11, 12, 13, 14], has materially strengthened this view.

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The present study is a part of a general programme of investigation of neuro-muscular disorders by electromyographic methods, and makes use of a technique for studying the electrical potentials of single motor units (groups of muscle fibres innervated by single neurones). Adrian and Bronk [15] first demonstrated that electrical potentials from the smallest functional unit of the neuro-muscular system, a group of muscle fibres and its controlling motor neurone, could be obtained from an intact human muscle by means of coaxial needle electrodes inserted into the muscle. Adrian [16], Smith [17] and Lindsley [18] have since described in some detail the characteristics of the responses of single motor units in normal human muscles.

APPARATUS AND METHOD.

The apparatus consisted of a six-stage transformer-coupled amplifier,[1] which drove either a loud speaker or a Du Bois oscillograph. The electrodes were of the coaxial type, consisting of a hollow steel hypodermic needle which served as a ground lead and a fine insulated wire cemented into its lumen which served as a grid lead.

When myographic records were made in response to electrical stimulation of the ulnar nerve, an isometric myograph was used. The arm of the subject was tightly bound, volar side down, to a splint-board in such a manner that the entire forearm and hand were immobile with the exception of the fifth finger, which extended over the edge of the board. The finger was enclosed in a snug aluminium thimble so that flexion could occur only at the metacarpo-phalangeal joint. The thimble was attached to the myograph lever and was flanked on each side by two vertical uprights which prevented the finger from moving sideways when it flexed.

The stimulating electrodes consisted of brass plates covered with canton flannel soaked in saturated NaCl solution. The small electrode (1 by 4 cm.) was bent to fit the curvature of the arm and was securely attached just proximal to the internal condyle of the elbow-joint and slightly medialward where it was found to stimulate the ulnar nerve most effectively. The large electrode (5 by 5 cm.) was attached to the calf of the opposite leg. Maximal stimulating shocks were provided by discharging through the subject a 1 μF condenser charged to 16 volts. A rotary interrupter afforded various stimulating frequencies.

DESCRIPTION OF CASES.

Case 1.—A male, aged 18, was admitted to the neurological service of the Massachusetts General Hospital in June, 1932. Fatigue and weakness had been noticed for ten months, although previously he had been as strong and active as other boys. He could walk only about 200 yards; could climb but one flight of stairs; fell often when he walked and could not get up alone; experienced difficulty lifting extremities; had trouble elevating self from a prone or supine position; felt drowsy and lethargic at times; experienced difficulty in chewing and swallowing.

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[1] An amplifier of this type distorts the wave form of the action potential appreciably, but is perfectly adequate for studying the responses of single motor units so far as rhythm and amplitude are concerned.

Physical examination revealed generalized muscular weakness without apparent atrophy; bilateral ptosis, more marked on the right; right facial weakness; external ophthalmoplegia; difficulty swallowing a thick barium meal; chest examination (thymus) normal; typical Jolly reaction in all muscles on faradic stimulation.

He improved slightly with ephedrine, and continued taking it in doses of from 1 to 3 gr. daily for a year. When ephedrine was stopped for a week he became worse. There were partial remissions and exacerbations, but when seen in the out-patient department in September, 1933, his condition was the same as on first admission. In October, 1933, he was again admitted to the hospital. There was still marked ptosis on the right, but his facial expression was slightly improved. Respiration was weak and shallow. He fatigued quickly upon alternate supination and pronation of hands. The extensors of the leg and the sterno-cleido-mastoids were especially weak. He reported that the hand, arm and jaw muscles became tired soon after a meal was begun.

He has continued to take ephedrine sulphate until the present time with some beneficial effect. In December, 1934, he was given 30 grm. of glycine daily with ephedrine. He continued this for one month without greater benefit than when ephedrine was taken alone. At present he is not able to climb more than one flight of stairs or walk but a short distance. He cannot raise his arms to the level of his shoulders. Grip on a hand dynamometer is between 5 and 8 kg. An intravenous injection of benzedrine sulphate (10 mgm. in 30 c.c.) had no beneficial effect. Prostigmin, on each of several occasions, has relieved practically all symptoms for a few hours.

Case 2.—Male, aged 64, admitted to neurological ward of Massachusetts General Hospital in November, 1934. The chief complaints were: difficulty in speaking and swallowing, dating from eighteen months, but with remissions during past sixteen months; regurgitation of liquids and an inability to bite and chew solid foods; difficulty in spitting and in holding the head erect; choking sensations and inability to breathe at times. There was no difficulty in writing and no marked weakness of limb or trunk muscles. Ephedrine was given from November 9 to 20 with improvement, the patient feeling considerably stronger. Ephedrine was omitted for one day with immediate return of difficulties in speech and swallowing. Ephedrine 1·5 gr. and glycine 30 grm. daily, have been taken during the past five months with marked improvement of strength in face, neck and jaw muscles. However, the patient still has some difficulty swallowing rapidly and in speaking clearly. Prostigmin completely relieves him of these difficulties for approximately three hours.

Case 3.—A female, aged 13, was admitted to the neurological ward of the Massachusetts General Hospital in March, 1934. Five months before entry ptosis of the lids appeared and diplopia shortly afterwards. She could walk and run, but tired quicker than other children; was unable to chew food satisfactorily; had almost complete ophthalmoplegia; was barely able to show her teeth and unable to close her eyes. The jaw muscles were weak, but the tongue protruded fairly well. The hand grasps were slightly weak and the biceps and triceps muscles were weaker than normal. No marked weakness of lower limb muscles was demonstrable, but she complained of weakness in her legs after walking or climbing stairs. The pupils were equal and reacted well to light; the fundi were unchanged; tendon reflexes were normal; there was a fine tremor of the extended fingers and slight ataxia: a typical Jolly reaction was observed in arm and hand muscles on faradic stimulation; chest X-rays were negative. Several trials with ephedrine, 1 to 5 gr. daily, have proved to be of little benefit. Chocolate is thought by the patient to have a beneficial effect. Prostigmin gave complete relief for a few hours.

Case 4.—A female, aged 15, first noticed difficulty in speaking five months before admission to the Massachusetts General Hospital in March, 1935. When speech was continued for a few minutes it became thick and unclear. One month later she noticed difficulty in swallowing, especially at the end of a meal. The difficulties in speech and swallowing have gradually grown worse. On admission she was able to read aloud only three or four minutes before becoming inarticulate. There was drooping of the eyelids and weakness of the facial muscles of expression. Regurgitation of liquids through the nose occurred at times. The muscles of the limbs were not weak but often felt tired. Her condition was always worse at the end of the day. Prostigmin temporarily improved her speech and facial expression very markedly.

MYOGRAPHIC AND ELECTROMYOGRAPHIC EXAMINATIONS.

When coaxial needle electrodes were inserted in the affected muscles of the four patients and responses of single motor units recorded during voluntary contractions, obvious differences were noted between the records and those obtained from the muscles of normal human subjects. The same regular rhythm was apparent, but there were wide variations in the amplitude of the single motor unit responses, which are not characteristic of the records obtained from normal human subjects (fig. 1). With the early onset of fatigue in myasthenia gravis, even during weak contractions, the amplitude of the repetitive responses of a single motor unit becomes more variable and the unit often completely fails to respond, without in any way altering the fundamental rhythm.

Fig. 2 shows typical examples from a series of records obtained at ten second intervals from the rectus femoris muscle of Case 1, during

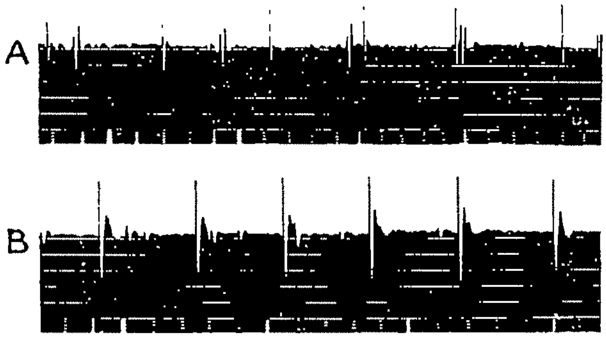

FIG. 1.—Typical single motor unit responses from normal human muscles during voluntary contraction, showing the regular rhythm and uniform amplitude. (A) from rectus femoris muscle showing two units at slightly different frequencies; (B) from tibialis anticus muscle. Time intervals at bottom of each record equal 0·028 sec.

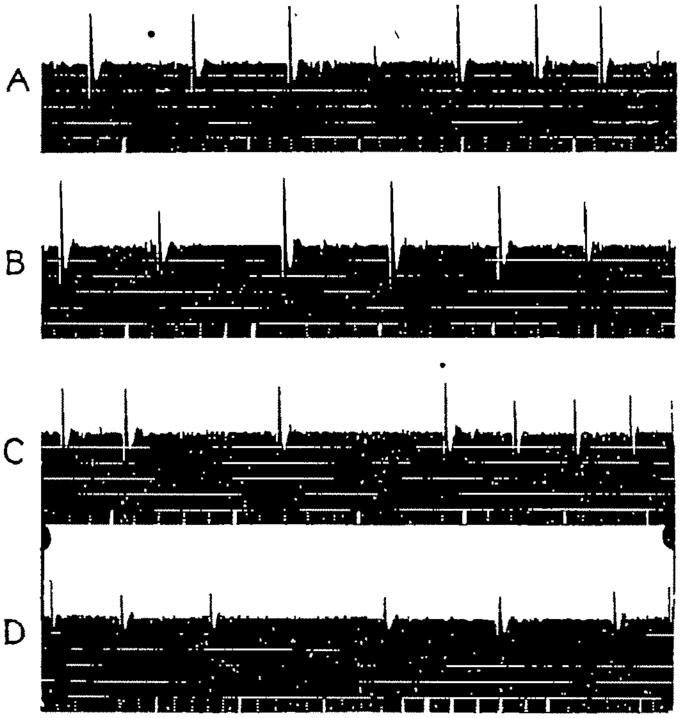

FIG. 2.—Responses of a single motor unit from the rectus femoris muscle of a myasthenia gravis patient (Case 1) during a weak contraction, showing the fluctuations of amplitude characteristic of this disorder. (A) at the start of the contraction; (B) after 40 seconds; (C) after 80 seconds; (D) after 170 seconds. Time intervals equal 0·028 sec.

a voluntary contraction (extension) maintained as long as possible. The muscles of this patient were all involved in the myasthenic condition, but the thigh muscles were particularly affected, so that he was usually able to maintain a contraction of this type only about two or three minutes before complete fatigue. The patient was sitting comfortably in a chair with one leg hanging over a padded cross-bar, the foot just clearing the floor. A rigid obstruction immediately in front of the ankle prevented actual shortening of the muscle or movement of the leg when voluntary extension was attempted. The needle electrodes were usually inserted to a depth of from 1 to 4 cm. and held securely in place by means of an adjustable holder attached to the leg.

Record (A) of this series, taken shortly after the start of the contraction, shows the rhythmic responses of a single motor unit. The first three responses are of uniform amplitude and do not differ from the normal. The fourth response and also the eighth are greatly diminished in amplitude. Record (B), obtained thirty seconds after the start of the contraction, shows further irregularity in amplitude, the second and sixth responses being diminished in size and the seventh being just barely visible. Record (C), taken after 140 seconds, shows some irregularity and a general decrease in amplitude of all responses with the complete absence of the third and fifth responses, although the rhythm is maintained as if they had occurred. The final record (D), obtained 170 seconds after the contraction began and just prior to complete fatigue, shows additional fluctuations of the responses and a general diminution of amplitude with absence of the fourth response.

Case 2, in whom the myasthenia was limited to the muscles of bulbar innervation, showed marked weakness and fatigability of the muscles of mastication, swallowing and speech. The neck muscles were also weak. With the needle electrodes inserted in the left sternocleido-mastoid muscle while the head was voluntarily turned to the right against restraint, records were obtained which show the same characteristic fluctuations in amplitude as in Case 1. Records were also obtained from the flexor digitorum sublimis muscle of the forearm during maintained flexion of the middle finger. This muscle was not noticeably involved in the weakness, and it is of interest that the single motor unit responses showed but very slight variations in amplitude, so little, in fact, that it was difficult to distinguish the records from those of a normal subject.

The same irregularity of amplitude of single motor unit responses has been observed in records obtained from the biceps and tibialis anticus muscles of Cases 3 and 4. In a record from the biceps muscle of Case 3, for example, during a weak voluntary contraction, the amplitude varied considerably twenty seconds after the start of the contraction and also during the next sixty seconds. At the end of 90 seconds the unit was responding only occasionally, and many responses were completely absent. At this point the patient was so fatigued that she could maintain the contraction no longer. Although in Cases 3 and 4 the greatest weakness was observed in the less accessible muscles of the face and neck, it is of interest that the records of single motor unit activity in other muscles of the body show the characteristic fluctuations of amplitude.

The rhythm of the single motor unit responses in all cases was as regular as that of normal human muscles and there were no variations in rhythm which correlate with the fluctuations of amplitude. Even where one or two responses were completely absent the regular rhythm of the unit was maintained and subsequent responses appeared "on time."

The effect of prostigmin.—Several recent reports in the literature have indicated the prompt and striking effect of intramuscular injections of prostigmin in temporarily relieving the symptoms of myasthenia gravis. Prostigmin has been tried in all four cases here reported and found to have the same remarkable effect described by others. The usual doses of prostigmin (3 to 5 c.c.) with atropine $\frac{1}{100}$ gr. have been given intramuscularly. The maximum effect is reached within thirty minutes and usually continues for about two to three hours, depending, of course, upon the severity of the case, the dosage given, and the amount of activity indulged in by the patient. The effect has usually passed off completely in six hours.

Five minutes following an injection (5 c.c.), Case 1 reported a feeling of tenseness in the facial muscles, particularly around the eyes. In ten minutes the ptosis of both lids disappeared and a remarkable change in facial expression was apparent. Twenty minutes after the injection the patient was able to raise his arms to the level of his shoulders or above his head, jump off the floor, arise easily from a prone or supine position and perform several acrobatic feats hitherto impossible. After thirty minutes his grip had increased from 6 kg. with the right and 8 kg. with the left to 31 kg. and 33 kg. respectively. Sitting in a chair with his leg over a cross-bar before the prostigmin was given, he was able to extend the right leg to a horizontal level only twenty times and the left twenty-five times, whereas thirty minutes after the injection he extended each leg sixty times without sign of fatigue.

Although Case 2 improved remarkably on ephedrine and glycine, speech and swallowing were still affected and there was weakness of facial and neck muscles. Following an injection of 3 c.c. of prostigmin with atropine $\frac{1}{100}$ grm., the eyes opened wide and facial expression improved. Before the injection he was able to drink water only by resting between swallows, whereas twenty minutes after the injection he could drink a glass of water rapidly and without hesitation. Speech returned to normal. The strength of grip which was thought to be normal before the injection remained the same. The duration of the relief was about four hours.

Case 3, before an injection of prostigmin, lacked facial expression and all the muscles of the face, neck and jaw were weak. There was almost complete ophthalmoplegia and diplopia. Speech was weak and indistinct. Following the administration of 3 c.c. of prostigmin with atropine $\frac{1}{100}$ gr., these symptoms were almost entirely relieved for a period of three hours.

Case 4, following a similar injection, became alert and wide-awake. Her eyes opened wide and facial expression improved greatly. She was able to read aloud for fifteen to twenty minutes without any difficulty, whereas before the injection she could read aloud only three or four minutes before speech became indistinct and impossible. She was able to hold her eyelids tightly closed and strongly resist attempts to open them, which she had not been able to do previously. Hand dynamometer readings increased from 22 kg. on the right and 20 kg. on the left before the injection to 35 kg. on the right and 32 kg. on the left, forty minutes afterwards.

Electromyographic records obtained immediately before the injection of prostigmin and again thirty minutes afterwards show that the single motor unit responses, which were irregular and often absent before, were consistently present and of quite uniform amplitude after prostigmin. These remarkable changes are shown in some typical records presented in fig. 3. In every case, responses of several different motor units obtained before prostigmin showed the typical irregularity of amplitude, whereas thirty minutes after the injection responses of single motor units in various parts of the same muscle showed consistent uniformity of response.

Pritchard [19] reported characteristic myographic tracings from the little finger of myasthenia gravis patients when the ulnar nerve was stimulated at various frequencies. He found, in such cases, that at high frequencies (80 to 500 per second) the myograph curve, unlike

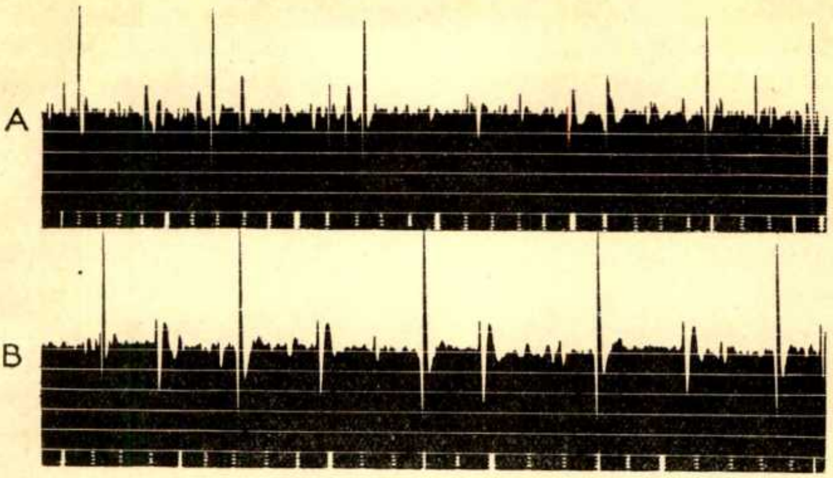

FIG. 3.—Records from the rectus femoris muscle of a myasthenia gravis patient before and after prostigmin. (A) typical single motor unit responses before, showing the irregularity of the amplitude and complete absence of the fourth response; (B) typical record 30 minutes after prostigmin, showing two units of regular rhythm and uniform amplitude. Time intervals equal 0·023 sec.

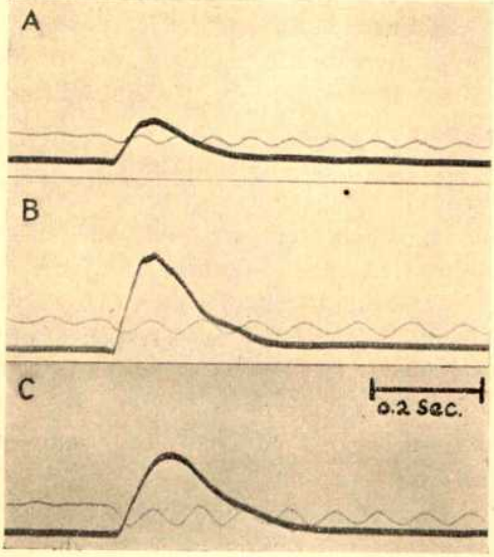

FIG. 4.—Myograph curves of flexion of fifth finger in response to single shocks through the ulnar nerve. (A) myasthenia gravis patient before prostigmin; (B) 30 minutes after prostigmin; (C) normal subject. Ignore faint wavy line.

that of a normal subject, failed to maintain its initial level and the tension gradually diminished with continued stimulation. The higher the stimulating frequency, the greater the rate of diminution. This he interpreted as an example of Wedensky inhibition. In later communications [10, 11] he has reported the effect of prostigmin in restoring the myograms of myasthenia gravis patients to normal.

Using a very similar technique, we have obtained myographic records from Case 1 and a normal control. Our results agree fundamentally, although not in all details, with those of Pritchard. His report [19], for example, indicated that for single shocks or low frequencies of stimulation (40 per second), the myograms in myasthenia gravis were essentially normal, whereas our records (fig. 4) show that

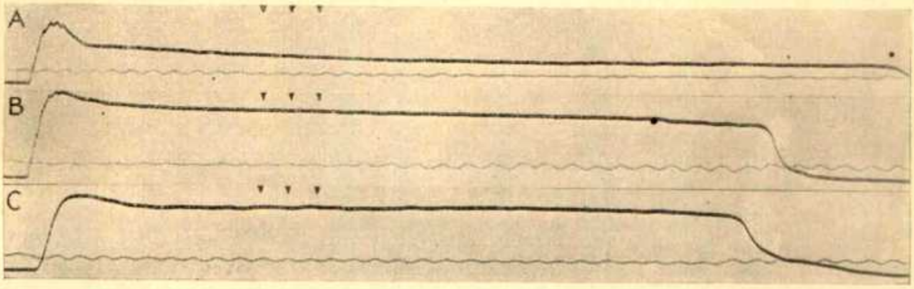

FIG. 5.—Myograph curves of flexion of fifth finger in response to repetitive stimulation (80 per second) through ulnar nerve for approximately 3 seconds. (A) myasthenia gravis patient before prostigmin; (B) 30 minutes after prostigmin; (C) normal subject. Time intervals at top of record equal 0·10 sec. Ignore faint wavy line.

the response to single maximal shocks before prostigmin (A), was much smaller than the response thirty minutes afterwards (B), or than that of the normal subject (C). It is obvious that prostigmin substantially increased the amount of tension developed in response to a single shock. Likewise, with frequencies of stimulation as low as 10 per second, the level of the myograph curve was in every case substantially increased by prostigmin. With higher frequencies of stimulation (80 to 480 per second) we have found that the myograph curve of the myasthenic patient resembles those described by Pritchard. Fig. 5 shows records obtained from the myasthenic patient before and after prostigmin and from the normal subject, using a stimulating frequency of 80 per second. Before prostigmin was given the myograph curve (A) rose to an initial maximum which was not maintained and although stimulation was continued for approximately three seconds, the curve gradually fell to a considerably lower level. On the other hand, thirty minutes after the injection of prostigmin the myograph curve (B) reached a much higher initial level and maintained it fairly well throughout the course of stimulation. The curve decreases slightly, but very closely resembles the curve (C) from the normal subject. The myograph curve of the normal subject maintains a level plateau during continued stimulation at this frequency. We have found, however, that at higher frequencies of stimulation (330 to 480 per second) the normal myograph curve fails to maintain its initial height and falls to a slightly lower level, which it maintains during the course of continued stimulation. The curve of the myasthenia gravis patient, in response to these higher frequencies, reaches an initial maximum which is less than the normal and rapidly descends to its base-level. Following prostigmin, however, the curve is similar to that of the normal subject.

DISCUSSION.

The fact that the motor unit in myasthenia gravis maintains its regular rhythm, whether its electrical response is a fraction of its original amplitude or entirely absent, indicates that the motor neurone is functioning normally and conveying a regular succession of impulses to the muscle. Therefore failure of response must be due to a blocking of the transmission of excitation at the " myoneural junction ", or to a prolonged recovery period of the muscle. The latter could hardly be the case, since in fig. 1 the frequency of the response is 10 to 13 per second, which would allow from 75 to 100 milliseconds between responses for recovery. In addition, a full-sized response often occurs immediately following one of diminished amplitude without change in the duration of the interval between responses.

The characteristic irregularities of amplitude of the action potentials of the single motor unit and the associated weakness and fatiguability of the muscles are therefore due to the failure of the nerve impulse to excite some or all of the muscle fibres controlled by the motor neurone. If the neurone sends branches to one hundred or more muscle fibres which compose a unit [20, 21], irregularity in amplitude would seem to result from a blocking of excitation to a variable number of the muscle fibres supplied by the neurone. This would also result in a similar variation of tension.

Following the administration of prostigmin (an analogue of eserine), the action potentials are restored to a consistently uniform height along with the return of normal strength. Likewise, the myograph curves of tension in response to single and repetitive shocks through the ulnar nerve show a substantial increase after prostigmin. Since it has been shown that eserine prevents the inactivation of acetylcholine by blood esterase [22, 23, 24], the above results strongly suggest that acetylcholine or a related choline ester plays an important part in the transmission of excitation at motor nerve endings in skeletal muscle.

In view of the many investigations (*see* Dale [25, 26]) which are rapidly supplying evidence of chemical mediation of excitation both at ganglionic synapses and at sympathetic and parasympathetic nerve endings on smooth muscles and glands, it is not surprising that this and other studies [27] point to a similar mode of excitation at motor nerve endings in voluntary muscle.

SUMMARY.

(1) Action potentials from single motor units of the affected muscles of four myasthenia gravis patients showed abnormally marked fluctuations in amplitude.

(2) The persistence of a regular rhythm of the single motor unit responses, although wide variations in amplitude occurred, indicates that the nerve is functioning normally and sending a regular succession of impulses to the muscle.

(3) Myograph curves of flexion of the fifth finger in response to stimulation of the ulnar nerve with single and repetitive shocks showed diminished initial tension which rapidly decreased with continued stimulation.

(4) Following intramuscular injection of prostigmin the symptoms of weakness and fatiguability temporarily disappeared, the action potentials were restored to a uniform height and the myograph curves became practically normal.

(5) These results are interpreted as strongly suggesting that acetylcholine or a related substance is liberated at motor nerve endings and takes part in the transmission of nerve impulses to voluntary muscles.

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THE PERIPHERAL NERVES IN CASES OF SUBACUTE COMBINED DEGENERATION OF THE CORD.

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IT has been suggested by many writers that some of the symptoms of subacute combined degeneration might be due to lesions in the peripheral nerves. But microscopical proof of the presence of such lesions has never been conclusive, although degenerative changes have occasionally been observed. Thus Russell, Batten and Collier found "very considerable degeneration both by the Marchi and Weigert-Pal method" in the nerve to the vastus internus muscle in their Case 1, and "some degeneration in the left sciatic and left anterior crural nerves, and more in the left than in the right phrenic nerve" in their Case 2. Von Noorden found considerable degeneration of the tibial nerves though not of the crural nerve in one case, and Mathieu reported a case in which the myelin sheaths of the sciatic nerve were beaded. Hamilton and Nixon made a careful study of the anterior tibial nerves in their cases by the Weigert, Marchi and Bielschowsky methods. They found definite degeneration by the Marchi method in six, and by the Weigert-Pal method in four of their cases. On the other hand, many authors (Lichtheim; Minnich, Nonne, Burr, Boedeker and Juliusberger) have reported that the peripheral nerves in cases studied by them were normal. In view of such conflicting observations it was considered worth while to re-examine this question.

METHOD AND RESULTS.

Peripheral nerves were obtained from a series of cases of subacute combined degeneration. In the early cases of this series the nerves were stained by Weigert-Pal, Marchi and Gros-Bielschowsky methods. These methods, though indicating an abnormality of the nerves in their peripheral branches were found to be in some ways unsatisfactory. The Weigert-Pal method failed to stain completely the finest myelinated fibres, which failure might result in a misleading appearance in a nerve containing a large proportion of small myelinated fibres. The Marchi

(Busch) method was unreliable for two reasons. First, it is well known that any stretching or handling of a small nerve may give rise to appearances in Marchi preparations which are almost indistinguishable from those of early degeneration. Secondly, it was considered unsatisfactory to use in chronic cases a method which only demonstrated progressive changes. The Gros-Bielschowsky method gave excellent staining of nerve fibres in celloidin sections. No definite lesions could be seen in nerves examined by this technique, even when the number of myelin sheaths appeared to be greatly reduced in sections of the same nerve stained by the Weigert-Pal method.

It was therefore decided to stain the myelin sheaths by placing the nerves in 1 per cent. osmic acid for twenty-four to thirty-six hours immediately after they were removed from the body. As it was considered desirable that an examination should be made of nerves obtained from living patients, as well as from post-mortem material, attention was confined to the terminal portion of the internal branch of the anterior tibial nerve which lies between the 1st and 2nd metatarsals. This nerve was dissected out with care and a portion removed under local anæsthesia from patients without causing any discomfort or disability. A piece about 2 to 3 cm. long was taken, and, after treatment with osmic acid, the central part was cut in paraffin, both in the longitudinal and transverse planes. The material examined in this way was taken from four cases of subacute combined degeneration of the cord (one at autopsy, the rest during life), two cases of alcoholic neuritis (one during life), and one of acute infective polyneuritis. Control material was taken from patients with cerebral tumour and cerebral arteriosclerosis dying at various ages. The diagnosis of subacute combined degeneration in the living patients was made only after adequate blood investigation had been carried out, such as blood-count, hæmoglobin content and a Price-Jones curve. When a megalocytic anæmia was found the reticulocyte response to liver therapy was tested. There was also in the three living patients an absence of free HCl after an alcohol test meal during which histamin was given subcutaneously.

In order to determine if demyelination of a nerve bundle had taken place, a count of the number of myelin sheaths per square millimetre of nerve in transverse section was made. This was done without difficulty in photomicrographs of nerve bundles enlarged to 800 or 1,000 diameters. A survey showed that whereas in five normals the nerve bundles from the nerve chosen contained from 5,000 to 10,000 myelin sheaths per square millimetre of cross section, counts of myelin sheaths in nerves taken from cases of subacute combined degeneration were rarely as high as 5,000 per square millimetre, and often much below this level. Reference to Table I clearly shows the poverty in the number of myelin sheaths in the nerves obtained from cases of subacute combined degeneration. It will be seen that a similar diminution in number occurs in the cases of alcoholic neuritis.

TABLE I.

NO.	COUNTS	MEAN	DIAGNOSIS
1 S.	2450		
	2920		
	3600	2990	Subacute combined degeneration of the cord.
2 W.	2160		
	3800	2980	Subacute combined degeneration of the cord.
3 H.	1700		
	4650		
	5000	3783	Subacute combined degeneration of the cord.
4 I.	3700		
	5080	4365	Subacute combined degeneration of the cord.
5 K.	1075	1075	Alcoholic neuritis.
6 H.	2860		
	3190		
	3460	3170	Alcoholic neuritis.
7 P.	5200	5200	Polyneuritis.
8 W.	6300		
	6500		
	7280		
	7870	6988	Hypernephroma.
9 B.	5560		
	7000		
	7260		
	9100		
	9600	7704	Cerebral softening.
10 D.	6600		
	7700		
	7800	7387	Hemimyoclonus.
11 B.	6400		
	6900		
	7200		
	7400		
	8900	7760	Cerebellar tumour.
12 F.	7800		
	8400		
	8750		
	9010		
	9050	8602	Pituitary tumour.

On microscopical examination the nerve bundles of the cases of subacute combined degeneration showed some separation of the nerve from its perineurium, and the appearance of fairly wide clefts in the substance of the bundles. This was also observed in nerves from normal subjects, but not to the same degree. It was obvious that this might result either from loss of nerve tissue, or from distension of the perineurium by œdema. In the latter case the reduction in the number of the myelin sheaths per square millimetre might be more apparent than real, although care was taken to exclude empty spaces under the perineurium from the planimetric measurements of the area of nerve examined.

It was therefore considered advisable to have some criterion other than the number of myelin sheaths per square millimetre in assessing the presence and degree of degeneration in these nerves. Accordingly an attempt was made to estimate the proportion of myelin sheaths of different sizes in this nerve obtained from cases of subacute combined degeneration and polyneuritis as well as from controls. Approximate measurements of the diameter of the myelin sheaths in multiples of 1μ were made, and the numbers were then tabulated according to size. The proportion of myelin sheaths of each size was then calculated as a

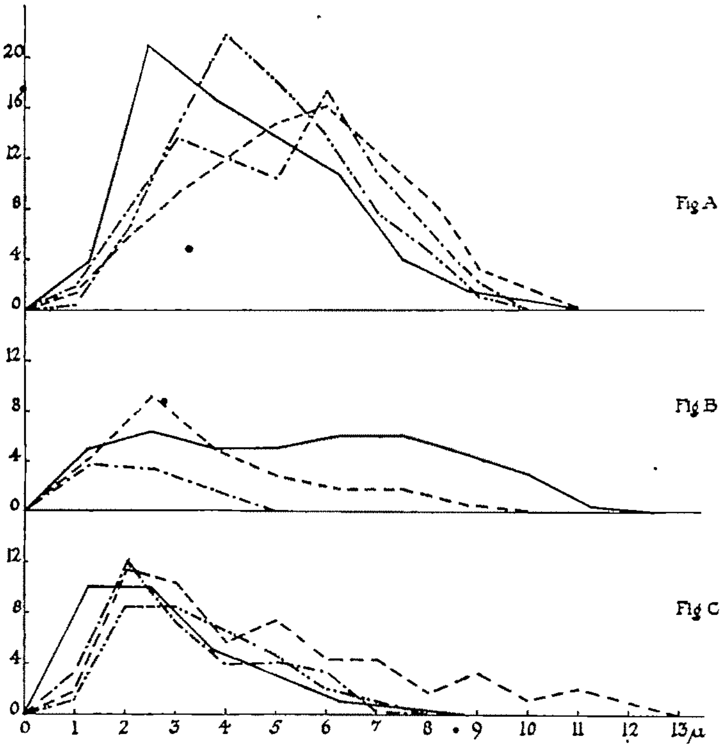

FIG. 1.—Curves of the number of myelin sheaths per sq mm. in the peripheral nerves from normals, A; in peripheral neuritis, B; and from patients with subacute combined degeneration of the cord C.

B. — . — Case 5.
— — Case 6.
—— Case 7.
C. — . — Case 1.
— . . — Case 2.
—— Case 3.
— — Case 4.

Ordinates represent number of myelin sheaths in hundreds. Abscissæ represent size of fibres in μ.

percentage of those in the whole nerve bundle. These percentages, corrected to the number of myelin sheaths per square millimetre, were taken to give an approximate estimate of the number at each micron of diameter per square millimetre of the cross section of the nerve. When the counts were charted as curves it was found that, whereas the normal nerves contained myelin sheaths ranging from 1 to 10 μ in diameter, with a preponderance of those between 3 and 6 μ, the nerves from cases of subacute combined degeneration contained very few sheaths of over 8 μ, with the great majority under 4 μ (fig. 1). It appeared, therefore, that either the larger myelinated fibres had suffered more than the smaller, or that there was a general reduction in size as well as in number of myelin sheaths. In the nerve obtained from the only post mortem case of subacute combined degeneration a similar preponderance of small myelin sheaths was found; but there were in this nerve a certain number of larger myelin sheaths, some of which measured up to 12 μ. It was noteworthy, in this case, that many of the myelin sheaths, instead of appearing as clear cut circles, presented a double contour or were filled up with darkly-stained material. Longitudinal sections of this nerve showed a considerable amount of beading and irregularity of contour of the myelin sheaths. It is important to note that, in this case, the course of the disease had been rapid, the first symptoms appearing seven months before death, and leading to a bed-ridden condition six weeks before death, which was due to embolism of the pulmonary artery. A similar appearance was seen in the nerve from the case of acute infective polyneuritis of six weeks' duration (Case 7). In the nerve of this case large myelin sheaths up to 12 μ were found, and considerable Wallerian degeneration of individual myelinated fibres was seen in longitudinal sections of the nerve. The similarity of the appearance in the nerves of these two cases suggest that the abnormally large circles, seen in cross section of both nerves, represented swellings of the sheath on rapidly degenerating nerves. It was unlikely to be the result of post-mortem autolysis as no other post-mortem material showed a similar change. The curves plotted from the nerves of cases of subacute combined degeneration were remarkably uniform except for that obtained from this post-mortem case. Curves of very similar type were obtained from two cases of alcoholic neuritis. In one of these there were so few myelin sheaths in some of the nerve bundles, and those present stained so poorly, that it was very difficult to make accurate measurements and counts; the curve charted is taken from the least affected bundle in the section.

DISCUSSION.

The great difference in measurements as well as in counts of myelin sheaths in the nerves of cases of subacute combined degeneration of the cord from those found in normal nerves may be accepted as evidence that there is a true degeneration of the peripheral nerves in this disease. As to the nature of this degeneration it has not been possible to form any definite opinion. The nerves examined by the Gros-Bielschowsky method have shown neither reduction in number, nor an alteration in the appearance of nerve fibres. It therefore seems unlikely that the axons are affected to any appreciable degree. Except in the rapidly fatal case of subacute combined degeneration of the cord to which reference has been made, there was very little abnormality in the contour of the myelin sheaths as seen in longitudinal sections and nothing was ever seen suggesting Wallerian degeneration. Nor is there any reference in the literature to the presence of Wallerian degeneration in subacute combined degeneration of the cord. On the other hand the preponderance of myelin sheaths of small size, as well as the poor staining of many of the myelin sheaths as compared with those in normal nerves, suggest that in subacute combined degeneration the nerve fibres suffer a general impoverishment of myelin. No doubt in severe and rapidly progressive cases Wallerian degeneration of individual fibres may occur, but this must be exceptional.

It has been stated that the appearance in the osmic acid sections might be interpreted as indicating œdema of the fine nerve bundles. That œdema of nerves does occur is known, and it is the rule in many forms of polyneuritis. The presence of œdema in the nerves of cases of subacute combined degeneration, if established, would therefore confirm rather than disprove the view that lesions of peripheral nerves are present in this disease. However, no definite evidence of œdema was found in celloidin sections of the peripheral nerves in any case of this series, although the Weigert-Pal sections of these nerves gave evidence of considerable loss of myelin sheaths. It is therefore not possible to explain these results on the basis of œdema of the peripheral nerves.

SUMMARY.

A. Peripheral nerves from normal people, from cases of subacute combined degeneration of the cord, and cases of neuritis have been compared microscopically.

B. It has been shown that the myelin sheaths are reduced in number in the nerves of patients with subacute combined degeneration, and that the reduction is of the same type, but not of the same degree, as that found in alcoholic neuritis.

C. The reduction in the number of myelin sheaths affects all sizes, but preponderates among those of large size.

It is a pleasure to express our thanks to our colleagues for permission to record these findings in patients who were under their care. To Mr. Harvey Jackson we are indebted for the skilful manner in which he removed the peripheral nerves under local anæsthesia. This work was carried out on behalf of the Medical Research Council.

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APPENDIX.

Case Histories.

Case 1.—S., male, aged 58, admitted under the care of the late Dr. Collier. He complained of tingling in the fingers for one year. Three months previous to admission he felt weak in his legs and the feet felt numb. On examination he was pale and sallow. There was no abnormality of the cranial nerves. The power of the arms and legs was good and no wasting was present. There was a striking inability to perform fine movements with accuracy in the hands, and he was ataxic in his gait. The arm and leg reflexes were normal. The plantar responses were extensor in type. There was a definite glove-and-stocking distribution of raised threshold to pin-prick and cotton wool. Vibration was lost in the legs. The cerebrospinal fluid was normal. Gastric analysis following histamin showed a complete absence of free HCl. The blood examination was as follows: red blood cells, 2,850,000; hæmoglobin, 92 per cent.; colour index, 1·6. The Price-Jones curve was shifted to the right. A good reticulocyte response was obtained following the administration of campolon.

Case 2.—W., male, aged 44. Nine years previous to admission he had an illness diagnosed as anæmia. From this he rapidly recovered, but one year previous to admission he became easily tired. This was associated with "tingling" of the finger-tips and was followed by a similar sensation in the toes. These subjective sensations spread up the arms to the elbows and up the legs to the knees. Walking became unsteady and a tight feeling round the waist developed. On examination he was found to be sallow and pale. Examination of the cranial nerves proved negative. Power and range of movement of the arms were good but the fine finger movements were clumsy. A similar condition was found in the legs. There was no wasting or fibrillation in the muscles. The arm reflexes were normal but both the knee and ankle reflexes were absent. The plantar responses were extensor. Sensory examination showed a glove-and-stocking alteration to pin-prick and cotton wool, while appreciation of vibration was lost in the legs. The cerebrospinal fluid was normal. There was no free HCl in the stomach contents after an alcohol meal with histamin subcutaneously. The results of the blood examination were as follows: red blood cells, 2,790,000; hæmoglobin, 92 per cent.; colour index, 1·6. The Price-Jones curve was shifted to the right. After treatment with campolon the reticulocyte count rose to 5 per cent. on the fifth day.

Case 3.—H., male, aged 56. Six years previously he observed that he was unable to feel the floor with his feet. The numbness in the feet progressed, spreading up the legs to below the knee. Two years previous to admission tingling and numbness commenced in the finger tips and spread up to the level of the wrists. At the same time he became unsteady on his feet. On examination he was slightly pale. The cranial nerves were normal. There was no marked wasting of the arms or legs, the power of which was good. The resistance to passive stretching was increased in the quadriceps. Fine movements of both the hands and feet were clumsily performed. The arm reflexes were brisk as were also the knee-jerks. The ankle-jerks were absent. The plantar responses were extensor. There was slight diminution to pin-prick over the digits of all four limbs, while vibration sense was lost in the legs. The cerebrospinal fluid was normal. Examination of the blood gave: red blood cells, 3,140,000; hæmoglobin, 82·3 per cent.; colour index, 1·3. The Price-Jones curve was shifted to the right. A good reticulocyte response was obtained after the administration of campolon. Gastric analysis showed an entire absence of free HCl after a subcutaneous injection of histamin.

Case 4.—I, female, aged 60, admitted under the care of Dr. Grainger Stewart. Seven months previous to admission, tingling and numbness commenced in the finger tips. There was little progress of symptoms till six weeks before admission, when the legs became weak and she had to take to bed fourteen days later. Associated with the weakness of the legs there was a sensation of "grit" in the soles. On admission, owing to her mental instability, the examination of the nervous system was undertaken with difficulty. There was no gross disturbance of function of the cranial nerves. There was no wasting of the arms or legs, all of which exhibited good power. The arm reflexes were normal; the knee and ankle jerks were very brisk, with ankle clonus. The plantar responses were extensor. The threshold for pain was raised in the legs and sense of position was very defective. There were 3,910,000 red blood cells with 93 per cent. of hæmoglobin in the blood,

PLATE XIX.

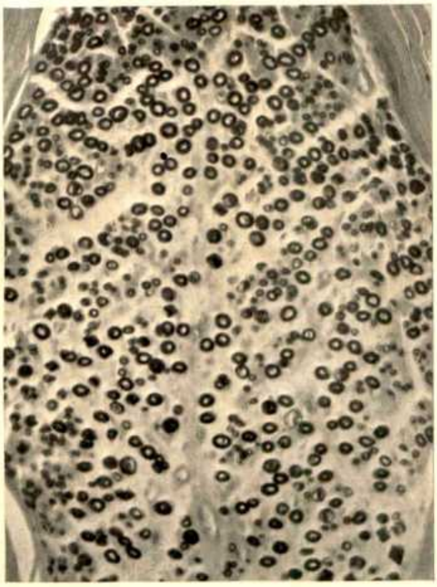

FIG. 2.

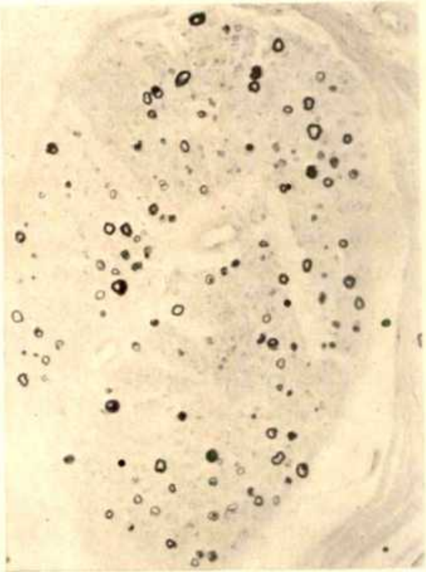

FIG. 3.

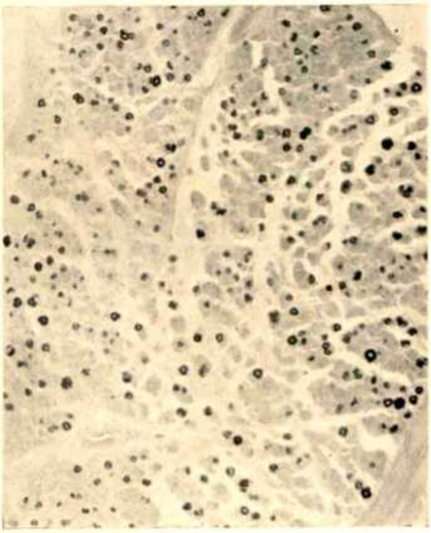

FIG. 4.

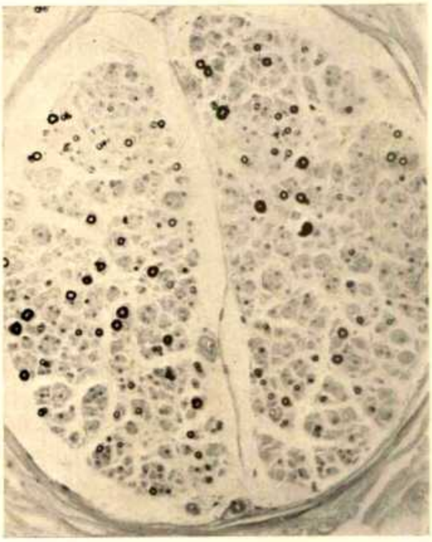

FIG. 5.

FIG 2.—Peripheral nerve from normal, stained with osmic acid. × 200.
FIG. 3.—Peripheral nerve from Case 6 of alcoholic neuritis, stained with osmic acid. × 200.
FIG. 4.—Peripheral nerve from Case 2 of subacute combined degeneration of the cord, stained with osmic acid. × 200.
FIG. 5.—Peripheral nerve from Case 3 of subacute combined degeneration of the cord, stained with osmic acid. × 200.

To illustrate paper by J. G. Greenfield and E. Arnold Carmichael.

giving a colour index of 1·2. Halometric readings indicated a halo of 8·1 μ. She rapidly went downhill and died fifteen days after admission. Post-mortem findings confirmed the diagnosis of subacute combined degeneration of the cord.

Case 5.—K., female, aged 35. For some years she had taken large quantities of wine daily as well as whiskey and beer. Seven months previous to admission she complained of pain in the soles of the feet and cramp in the calves, and during the last six months had been unable to walk. Two months previous to hospital treatment she developed weakness in both hands, and recently had had a very considerable loss of memory. On examination there was a fine irregular nystagmus on lateral deviation of the eyes. There was marked wasting of both forearm and hand muscles with great weakness. The legs were wasted below the knees and bilateral drop-foot was present. All the deep reflexes were absent and no plantar responses were obtained. The muscles of the forearms and calves were exceedingly tender and there was an associated glove-and-stocking anæsthesia to pin-prick. The protein content of the cerebrospinal fluid was 110 mg., otherwise the fluid was normal. The blood examination gave normal results. On appropriate treatment she made a good recovery, the tendon reflexes returning in the arms.

Case 6.—H., male, aged 62, admitted under the care of Dr. Hinds Howell. As manager of a licensed victualler's business, he had taken considerable quantities of alcohol. On two previous occasions he had suffered from delirium tremens. One month before admission he went off his food. During the fourteen days immediately preceding his admission, he had become incoherent and mumbling in his speech. Examination was difficult owing to the mental state. No gross defect of function of the cranial nerves was observed. He moved his arms freely, but his legs were flail-like and very tender to pressure. The arm reflexes were present as were the knee-jerks, but the ankle-jerks were absent. No plantar response was obtained. Sensory tests were impossible. The cerebrospinal fluid was normal. He died four days after admission.

Case 7.—P., female, aged 26, admitted under the care of the late Dr. Adie. Six weeks previous to admission she was seized with sharp pains in the legs. Three weeks later she had definite weakness of arms and legs with numbness of the legs up to the calves. At this time she was unable to walk owing to the weakness of her legs. A few days prior to admission she developed difficulty in swallowing and breathing. On examination of the cranial nerves there was weakness of the facial musculature. There was extensive flaccid weakness of all four limbs without any gross wasting. The tendon reflexes were all absent and no plantar responses were obtainable. There was a glove-and-stocking anæsthesia to pin-prick. She died suddenly two days after admission. The post-mortem diagnosis was acute infective polyneuritis with severe degenerative changes, including Wallerian degeneration, in the peripheral nerves.

THE SUBPIAL RESECTION OF THE CORTEX IN THE TREATMENT OF JACKSONIAN EPILEPSY (HORSLEY OPERATION) WITH OBSERVATIONS ON AREAS 4 AND 6.[1]

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THE purpose of this paper is to draw attention to an operation first suggested by Victor Horsley for the treatment of athetosis, which I have found most effective both for this condition and, to an even greater degree, for Jacksonian epilepsy.

In reviewing my cases of Jacksonian epilepsy extending over a period of twenty-five years, I find that I have performed this operation eleven times, and that there were eleven other cases on whom, in the light of my present knowledge, I feel that I should have carried out the same procedure.

Of the eleven cases operated upon, nine are cured, one has had a recurrence, and one died four weeks after the operation, so that in this case it was too early to speak of end-results, but during the time the patient lived, she was free of athetotic movements (Case 1).

The eleven cases that constitute the basis of this report were selected from a series of 189 cases of supposed focal epilepsies, but in this series no cases are included in whom Jacksonian convulsions were due to a brain tumour.

Of these 189 cases, 120 were discarded because of insufficient evidence that would justify the diagnosis of focal epilepsy. This conclusion was reached after thorough examination and, whenever possible, observation of the convulsions themselves by a trained observer, either a doctor or a nurse. The remaining sixty-nine cases were operated upon, and may be divided into three groups :—

First group.—Eleven cases of typical Jacksonian convulsions with extensive cortical degeneration.

Second group.—Nineteen cases of typical Jacksonian convulsions with definite focal scars.

Third group.—Thirty-nine cases in whom at operation no gross pathological lesion could be seen.

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[1] Read at the Meeting of the Second International Neurological Congress, London, England, July 29 to August 2, 1935.

In the first group, nothing was accomplished by operation because the entire or greater portion of the cortex was involved. The degeneration was very extensive, often containing huge degenerative cysts with areas of yellow gelatinous tissue. Most of these patients, besides having convulsions, showed mental deterioration.

In the second group, operation had to be very radical in order to remove the scar completely and, in several instances, the resection was carried down into the ventricle according to the suggestion of Foerster.

In the third group (thirty-nine cases) no pathological lesion could be seen grossly at operation, nor did subsequent histological study of the cortex, in those cases in which some of it was removed, show any abnormality.

This is the group of which I particularly wish to speak. In eleven of these cases, in whom the convulsions were definitely focal, I did a subpial resection of the cortex according to the method used by Victor Horsley and described by him in his Linacre Lecture in 1909. By this procedure it is possible to remove accurately an isolated convolution without encroaching upon a neighbouring area. On the other hand, if the resection of the cortex is undertaken through the intact pia and its intact vessels, it is impossible, in man, accurately to isolate and remove one convolution. In the remaining twenty-eight cases, I did not attempt this procedure. When I found no gross evidence of cortical abnormality, I hesitated to do this unless I was absolutely certain that I was dealing with a true Jacksonian convulsion. In each of these patients, it is true, the convulsions always had the same pattern, but they spread so rapidly and became general that, in the presence of a normal-looking cortex, I was uncertain whether I was justified in considering the convulsion a true focal one. In eleven of these twenty-eight cases, as I have reviewed them recently, in the light of our results I feel I was too conservative and should have done a subpial resection. I had not realized until I analysed these cases for this paper that in those in which I had resected the cortex, the convulsions had been stopped in all but one instance. Three of the patients who were operated upon for local athetosis had athetotic movements identical with those described in Horsley's case, which I was fortunate enough to see while working with him. In all three of these patients (Cases 1, 4, 7) the athetosis was stopped, but, as one patient died four weeks later following another operation, the period of observation was too short to know what the final outcome would have been.

In carrying out the resection of a convolution, it is all-important to remove the entire centre, arm or leg, as the case may be. In three of my cases the arm was not completely paralysed after the first operation (Cases 2, 3 and 7); therefore I reoperated and removed a larger area. In all three instances I found at the second operation, upon stimulation of the cortex, that I had left part of the arm centre. The histological examination of the areas removed was made for me by Professor James Lee O'Leary, of the Department of Cytology, of Washington University, who found that all but one of the specimens were motor cortex, Area F A gamma, the term applied to it by Economo and so designated because it contains some Betz cells.

In 8 of these 11 cases the convulsions began with a movement in either the arm or leg. The area removed was what is generally spoken of to-day as Area 4. In one case the convulsions definitely were preceded by a sensory aura in the hand, and in this case I removed the post-central gyrus opposite the arm centre. Nine of the ten patients have been free from convulsions; the one who had his post-central gyrus removed has been well for eleven years, and, during the past five or six years, has carried on his work as Professor of Physiology in one of our medical schools.

These cases in which the cortex looked normal to the naked eye and showed no demonstrable pathological changes have given us an unusual opportunity to observe the change in the cortex that occurs just before a convulsion begins. It has happened in many instances that, while searching for a centre with the electric current, we set off a convulsion. Over and over again I have been able to warn my anæsthetist that a convulsion was starting because of the change in the colour of the cortex. This change has invariably been an hyperæmia. Only once have I seen the preliminary pallor which, it has been claimed by some neurosurgeons, is the first observable change that occurs when a convulsion starts (Case 7). Formerly we used a bipolar electrode with a faradic current, but in the last few years have followed the suggestion of Foerster and have used unipolar stimulation with the direct current. The single shocks have the advantage, as he pointed out, of enabling one more accurately to outline a centre without exhausting or irritating it unduly. When a centre receives too much stimulation it becomes hyperactive and convulsions are initiated which obscure the picture and prevent an accurate ablation of the cortical centre.

These cases of resection have given us an opportunity of checking an important physiological question that is still somewhat unsettled, namely, the difference between the loss of function resulting from the removal of the precentral gyrus as compared with removal of the intermediate precentral gyrus, in other words Area 4 and Area 6. In this series Area 4 was removed ten times. Where a complete paralysis resulted, the length of time before the extremity recovered varied considerably. Usually movements began to return in a week or ten days, while, in a few cases, recovery was much slower. In one patient only slight elbow movements had returned at the end of five weeks. In only one case in this series was there a flaccid paralysis at any time after operation. The grasp reflex was tested in only one or two cases who had been operated upon in recent years, but in none was it found to be present. The absence of this reflex would be in accordance with Fulton's idea of the function of the premotor cortex, but our results do not support his contention that there is, at first, a flaccid paralysis following a removal of the motor cortex.

As only one convolution was removed in each case, we may conclude that the precentral convolution varies in the number of efferent impulses to which it gives rise; thus, if an adjacent convolution contains more efferent fibres earlier recovery may be expected. In regard to the extent of recovery of function, it was invariably observed that recovery of the fingers was much less complete than that of the shoulder, elbow and wrist. Concerning the extent and type of sensory disturbance following removal of Area 4, it was noted in several instances that there was some disturbance in accurate localization, loss of accuracy in recognizing compass points, and what I like to call incomplete astereognosis, due, I believe, to the sensory disturbance. To say that a patient has true astereognosis, there must be no other evidence of a sensory disturbance. I have seen this occasionally, but, in my experience, a pure astereognosis is rare.

Comparing the results in these cases with the results in the cases of wide excisions of scars, we find that where no scar was present the results are distinctly better. Only ten of the nineteen cases of scar excision have been without convulsions for a number of years. Some of the other nine cases have had a return of their convulsions, and some, unfortunately, have been lost sight of.

To speak of a patient who has had Jacksonian epilepsy as cured is an unwarranted statement, for we all know that patients may be free from convulsions for a long time, a number of years, and then the convulsions may recur as a bolt out of the blue. Only those patients may truly be said to be cured who, up to the time of their death from some other cause, years later, have been free of convulsions.

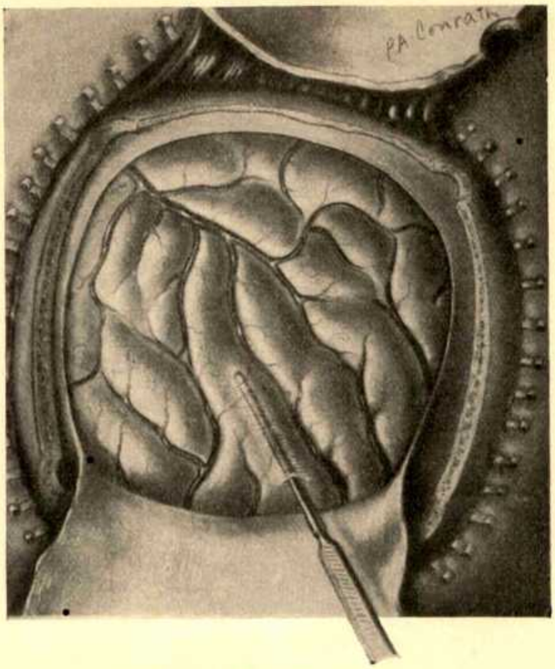

FIG. 1.—Method of freeing the pia.

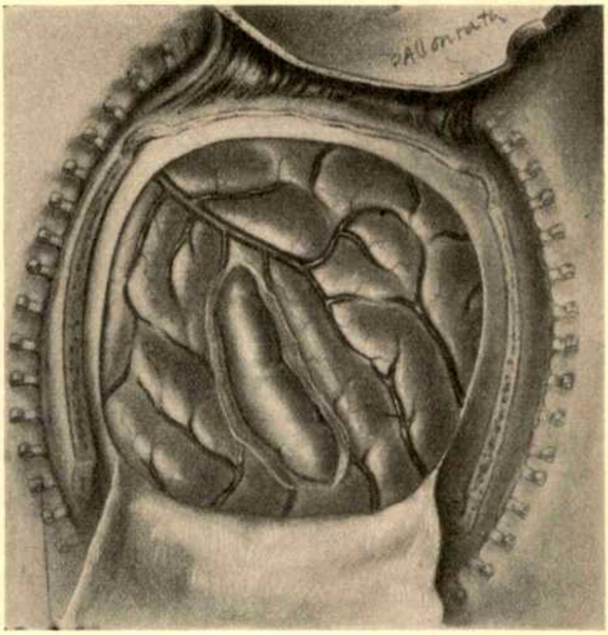

FIG. 2.—The convolution completely freed after the pia arachnoid has been pushed back with cotton pledgets.

It requires a little courage, I have found, to remove what appears to be a normal-looking cortex; but in the light of the experience herein cited, if I am convinced that I am dealing with a true Jacksonian epilepsy, I now have no hesitation in carrying out a subpial resection of the cortex. This procedure I have designated the Horsley operation.

Case 1.—E. F., aged 17, January 11, 1912, Barnes Hospital, No. 149.

At the age of 5 the patient had pertussis and following this developed athetosis in the right upper extremity and to some extent in the lower. The entire right arm and hand were in constant motion. At times the movements became very violent. Reflexes were not exaggerated. There was also movement of the right leg but not as marked.

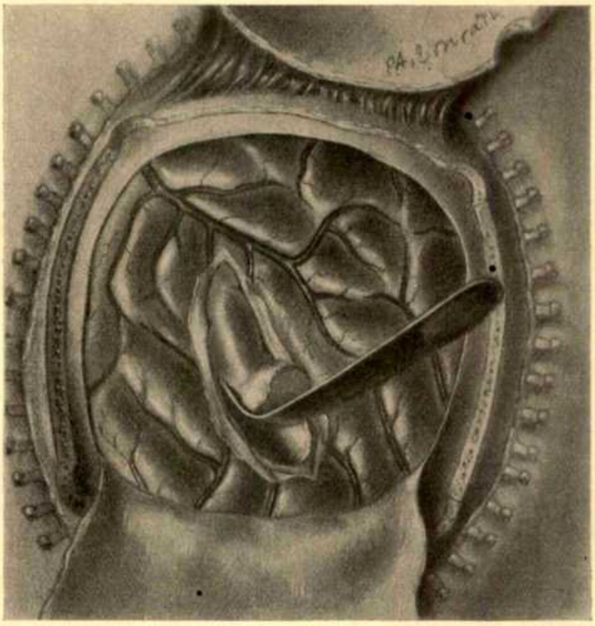

FIG. 3.—Removal of the convolution after the pia arachnoid has been pushed back. This is an absolutely bloodless procedure.

Operation January 23, 1912, under ether anæsthesia. A flap was turned down on the left side. Subpial resection of the arm centre was carried out. The arm, following this, was completely flaccid. Reflexes were not elicited. Athetoid movements ceased.

The patient was so pleased with the result that she requested something be done to stop the movements of her leg. Because of the location of the leg centre under the longitudinal sinus and the difficulty of exposing it, as well as because of a discussion to the effect that posterior root section would stop athetosis just as cortical excision did, on February 15, 1912, a laminectomy was done under ether anæsthesia, and the posterior root of the second, third, and fifth lumbar and the second sacral were cut. When the patient recovered from the anæsthesia, the convulsive movements of the leg were exactly as before operation. The patient developed an infection and died of a meningitis two days later.

Case 2.—W. J., aged 29, September 18, 1915, Barnes Hospital, No. 2350.

Complaint: Convulsions present for four years. Examination was practically negative. Reflexes before operation were normal with normal plantar responses. Four attacks were seen in the hospital which began with twitching in the left hand and then spread; therefore, operation was decided upon. The Wassermann reaction was negative.

Operation October 6, 1915, under ether anæsthesia. The arm centre was identified with the faradic current. The pia was split and the cortex excised. Patient had several post-operative convulsions, but there was no weakness of the left hand. Evidently the operation did not remove enough of the cortex, so the patient was re-operated upon six days later. On restimulating it was found that below the area of excision, there was a response by contraction of the face, and above this there was a response from the hand, forearm, and shoulder. This area was excised subpially.

The left hand became weaker after operation. Dynamometer on October 14, left 75, right 115 ; on October 18, left 90, right 115. There are no details in the post-operative notes regarding movement of fingers as compared with the rest of the arm. After a week the hand was getting stronger. A month later the left hand had regained its strength practically completely.

Case 3.—C. T., aged 27, May to November, 1917, Barnes Hospital, Nos. 4181, 4654, and 4707.

Present illness: Six months before admission the patient was kicked in the head on the left side by a mule. He was unconscious and was operated upon for compound fracture of the skull. He had a convulsion the night after the accident and then three months later began to have convulsions which commenced in the thumb.

The patient on examination had a partial motor aphasia, slight cortical facial weakness and normal reflexes. Because of the epilepsy he was operated upon on May 23, 1917, under ether anæsthesia. Adhesions were freed and a fat pad inserted.

The attacks were not relieved; therefore the patient was readmitted in October, 1917, still having convulsions. Operation on October 12 under ether anæsthesia. Fat pad found densely adherent to the cortex and removed. On account of the dense adhesions it was difficult to identify the precentral gyrus, but an area from which movement of the opposite extremity was obtained was excised by subpial resection. It was impossible to identify the thumb centre.

Following this operation the patient had some indefinite sensory disturbance but no paralysis of the hand, indicating either that the area removed was not Area four (4) and that the contraction we had obtained upon cortical stimulation was due to spread of the current, or that I had not removed enough of Area four (4).

The patient was therefore readmitted on October 27, 1917. Operation November 5, 1917, under ether anæsthesia. On stimulation it was found that I had not removed the entire precentral gyrus. This was removed, and following this the patient had a complete paralysis of his upper extremity. After four weeks the patient began to move his arm, first the shoulder girdle muscles. A letter received from him a month later stated that movement in his arm had improved and he was now able to move his fingers. No description as to whether the extremity was spastic or flaccid, or the character of the reflexes is available.

Case 4.—G. S., aged 27, April 29, 1920, Barnes Hospital, No. 8715.

Right hemiplegia at age of 8 which developed after an attack of typhoid fever. The lower extremity improved, but the upper extremity developed athetosis. The reflexes in both arm and leg were increased and ankle clonus was very marked; two-point discrimination test indicated no difference between the right and the left arms. When the patient became excited the left arm went into violent athetoid movements. Operation May 3, 1920, under ether anæsthesia. The arm centre was identified as well as the leg and face centres. A subpial resection from the edges of the leg centre down to the face centre was carried out.

Following operation the patient had complete loss of movement of her right arm. The athetoid movements had stopped. There was slight motor speech disturbance for a few days after operation, which had disappeared on the fifth day after operation; it was evidently due to œdema. Two-point discrimination test showed definite disturbance, but there was no other evidence of a sensory loss. The patient was discharged on May 18, 1920; she had begun to move her arm quite well but no athetoid movements recurred.

Case 5.—C. M., aged 15, July 17, 1920, Barnes Hospital, No. 9047.

At the age of 2 years the patient fell 6 ft. striking his head on a nail. At the age of 9½ he had his first convulsion (focal epilepsy). His attacks were observed in the hospital by a nurse. They began with the neck and head being drawn to the left and twitching of the left side of the body beginning in the left arm, then the left leg, and then the convulsion became general. Reflexes in the arm were overactive, with slight weakness of the left side, but no sensory disturbance.

Operation, July 21, 1920, under ether anæsthesia. On opening the dura there was thickening of the arachnoid. The arm centre was located behind the area of arachnoid thickening. The arm centre was not as accurately outlined as I should have wished because of the scar.

After operation there was no weakness of the movements about the shoulder, but there was weakness of the biceps and triceps and all movements in the forearm and fingers disappeared. Two-point discrimination below the elbow was impaired. On July 29 the strength of the left hand was improving.

Movements of the fingers at the time of discharge were still impaired. Patient when last heard from had had no convulsions.

Case 6.—C. W., aged 28, January 29, 1924, Barnes Hospital, No. 17056.

On November 5, 1922, the patient was in an automobile accident and sustained a comminuted fracture of the skull in the right parieto-occipital region. He was operated upon and a subdural clot removed. Nine months after the operation, while on a holiday in the mountains, he had his first convulsion. As he was a physician he was able to observe his attack very carefully. From this time on he had a convulsion every month for four consecutive months. The convulsive seizure was preceded by an aura as if his left forearm felt strange and did not belong to him. The attacks lasted from eight to thirty minutes. There was twitching of the fingers with systematic flexion extension movements. At the end of this time the patient became unconscious, the period of unconsciousness varied from eight to twelve minutes, and was followed by post-epileptic automatism lasting about ten minutes. Large doses of luminal did not control the attacks.

Operation, January 30, 1924, under ether anæsthesia. There was a dense scar between the scalp, bone and site of the old fracture. There was an area 5 by 5 cm. where there was a dense scar attached to the cortex. Cortical stimulation revealed that the motor area was entirely in front of the scar. The entire area involved with the scar was therefore excised, subpial resection being done. Forty-eight hours later the patient had a left facial weakness with flaccidity of the left arm and leg and an ankle clonus. The patient was drowsy and the pulse had dropped to 55. Evidently a clot had formed. On reopening the flap a moderate extradural clot was found, not enough to explain the symptoms. On opening the dura, the site of the cortical excision was filled with a huge blood clot. This was washed out and a silver clip put on a small bleeding spot.

The patient had one convulsive movement of the left hand two days after the second operation, then made an uneventful recovery. For the past five years the patient has held the Chair of Professor of Physiology at a Mid-Western medical school. He has never had a return of symptoms, either sensory or motor.

Case 7.—A. W., aged 22, October 12, 1928, Barnes Hospital, No. 17388.

Patient sustained a birth injury and from a few days after birth had athetoid movements of the right hand and forearm. She only began to walk at the age of 2, and talking was somewhat retarded. At the age of 12 she had her first convulsion which involved the face and the right arm. It was followed by a period of unconsciousness which lasted about an hour. A typical convulsion was described as beginning with a peculiar drawing sensation in the right side of the face, followed by drawing of the mouth to the right, quivering of the right arm and then tonic contraction of the arm and hand, the leg was very slightly involved. The patient frequently bit her tongue. The patient then combined athetotic movements of the right hand with typical Jacksonian convulsions beginning in the face and spreading to the hand.

Operation, October 15, 1928, under local anæsthesia. A left-sided craniotomy was carried out. It was somewhat difficult to locate the arm centre with the faradic current; more stimulation than usual had to be used. Finally the patient had a general convulsion. The cortex became typically pale and then, as the convulsion advanced, hyperæmic. Subpial resection of the cortex was carried out, extending from the abdominal centre right down to and including the wrist centre.

Following the operation the arm was spastic but not completely paralysed. Therefore four days later the wound was reopened under local anæsthesia, and on stimulation part of the arm centre was found still intact. This was excised by the same technique. Following this operation there was complete paralysis of the arm, forearm and hand. The hand was spastic. Occasional slight athetotic movements were still noted at the time of discharge. A letter from the patient a year later stated that she had been free of convulsions for a year, but following fright over a fire she had had one convulsion.

Case 8.—G. S., aged 18, May 8, 1931, Barnes Hospital, No. 29510.

Ten years ago the patient had a severe fracture of the skull. He was operated upon three times for the skull defect. For the past seven years he has had focal convulsions beginning in the right arm and spreading to the leg; the face was never involved. Following the convulsions the patient has weakness of the right upper extremity and of the toes. No sensory disturbances were present. No weakness existed between attacks. At the time of admission the patient was practically in a state of status epilepticus, having convulsions of the right arm every few minutes. It was impossible to control these with hypnotics. Therefore cortical excision was decided upon.

Operation, May 12, 1931, under local anæsthesia. On location of the arm centre with the galvanic current repeated convulsions were started. The cortex looked normal. The face centre was located higher than usual. Subpial resection of the cortex was not as neat a job because of the numerous vessels which had to be coagulated. At the end of the operation the patient was unable to move either his arm or his leg. The morning after operation the patient has some movement of his leg, but no movement of his arm whatever. He made an uneventful recovery. Occasionally he had a peculiar feeling in the right arm, but no convulsive movements were noted. At the time of discharge on May 30, there was no return of function in the arm. A note a year later stated that the boy used his hand perfectly but said that it was "dumb." He had no attacks since the operation. Occasionally he had peculiar sensations in his right hand which he described as twitching but no convulsive movements noted.

Subsequent history: One year later the patient began to have convulsions which have slowly become more frequent, and about April, 1935, he began to have increasing weakness of his arm and speech difficulty.

Patient was last seen in June, 1935. At this time he had slight convulsive twitchings of his right arm but no true convulsions; there was some hesitation of speech which is the residue of an old sensory aphasia.

Case 9.—L. F., aged 52, June 12, 1933, Barnes Hospital, No. 38823.

Patient was shot in the head one and a half years ago. One year later he developed right-sided convulsions and had six in all. Physical examination revealed right-sided hemiparesis, exaggerated reflexes in the arm, particularly in the wrist, slight ankle clonus, Babinski and Oppenheim responses, a suggestion of patellar clonus on the right, and the right abdominal reflex was less than the left. The convulsion was typically Jacksonian, beginning in the right hand and arm and extending to the shoulder. From the description it is not clear whether the sequence is arm to face or arm to leg. No sensory disturbance was present.

Operation, June 15, 1933, under local anæsthesia. The arm centre was located with the galvanic current. Stimulation started a convulsion. Subpial resection of the arm centre was carried out. All the rest of the scar tissue was then excised with the electric knife down to normal brain tissue. The ventricle was not opened.

There was complete paralysis of the hand but some movements in the arm and slight right facial weakness. At discharge on July 4, 1933, there was no return of movement in the hand, but movements of the arm were stronger. No evidence of spasticity in the arm. Patient has had no convulsions since discharge.

Case 10.—L. L., aged 40, May 10, 1934, Barnes Hospital, No. 43337.

Past history negative. For the past three months the patient has had Jacksonian convulsions involving the left arm and leg. Shortly before admission he began to limp and had weakness of the left leg and foot. Reflexes in both arms were perfectly normal. Neurological examination revealed no disease. A tumour, possibly an angioma, of the cortex was considered as a possibility. The cerebrospinal fluid was normal. Repeated attacks observed in the hospital always began in the left arm.

Operation, May 12, 1934. Under avertin a flap was turned down on the right side, the cortex looked normal. It was impossible to locate the arm centre with the galvanic current so that the faradic current had to be used. It was then possible to outline Area 4. A subpial resection of the cortex was carried out.

Following operation there was complete loss of movement of the arm and slight involvement of the flexion movements at the hip, but otherwise the leg was not involved. Reflexes in the left arm were perfectly normal; no flaccidity was noted. For three weeks after operation the patient had no movement in the arm whatever, but on June 5, flexor movements of the fingers and elbow were first obtained. The flexor movements increased in strength, the extensor movements were slow in recovering. At the time of discharge the patient had recovered only moderate use of his extremities. Since discharge there have been no convulsions. Power of the arm has never become normal, especially of the hand.

Case 11.—W. A., aged 11, October 4, 1934, St. Louis Children's Hospital, No. K-2199.

Jacksonian epilepsy beginning in the right hand with sensory aura and involving the right arm since the age of 3. The attacks were checked by luminal. Lately convulsions have been more frequent and more severe, but without loss of consciousness. Recently slight hemiparesis, mostly of the right upper extremity, appeared. Sensation was normal, including two-point discrimination on both sides. Patient walks with a slight hemiplegic gait. Evidently a focal epilepsy involving the arm centre.

Operation, October 10, 1934, under avertin anæsthesia. A broadened post-central convolution was found which was harder than normal but looked like normal brain tissue. This broadened convolution was found to contain the arm centre and a subpial resection was done.

After operation all movements of the upper extremity were absent except shrugging the shoulder. Biceps and triceps reflexes were normal; there was slight facial weakness, but no involvement of the leg. On October 13 the wound was reopened because of a moderate-sized extra-dural clot. The patient was discharged on October 28. At discharge there was poor movement in the right upper extremity; the greatest difficulty was in the extension of the wrist and extension of the fingers. Two months later movement of the arm had markedly improved, but there was still impairment of the finer movements of the fingers.

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NOTICES OF RECENT PUBLICATIONS.

Handbuch der Neurologie. Herausgegeben von O. BUMKE and O. FOERSTER. Berlin: Julius Springer. 1935.

The aim of the Editors of this system of neurology is to furnish a comprehensive and up-to-date series of volumes which will include all our latest knowledge in every branch of neurology. They have succeeded in collecting a noteworthy band of contributors, mostly from Germany it is true, but many from other countries, who can write authoritatively on the subjects allotted to them. The material is ready for publication, and it is stated that volumes will appear each month until the whole system is complete at the end of 1936. There will be in all seventeen volumes, and the price at time of publication will be 1260 RM., which will be considerably increased later. The cost is certainly high, but the system promises to be, for several years at least, the most complete work available in any language. The volumes now available for review are splendidly produced, the paper is good, the type is clear and legible, and the illustrations are well chosen and excellently reproduced.

Band I.: *Anatomie.* Pp. 1152, with 585 illustrations. Price RM. 120.

The first volume is entirely devoted to the anatomy of the peripheral and central nervous systems. It is thoroughly up to date and certainly includes all available anatomical facts which will be required by the clinical and research neurologist. It is profusely illustrated; there is, in fact, an average of at least one figure for every two pages, and a comprehensive bibliography at the end of each chapter. A very full index of authors and subjects is also provided.

It is impossible to give an adequate review of the contents of this volume, but a list of its subjects and of their authors will serve to indicate its scope. In the first chapter Rose gives an excellent but concise description of the embryology and development of the nervous system, a subject the importance of which is often lost sight of in the study of anatomy and in interpreting the relation of clinical symptoms and structural lesions. M. Bielschowsky deals with the histology of nerve cells and fibres, of the neurologia, and of the blood-vessels and lymph paths, and then defines the general principles of the pathology of these structures. He also discusses the neurone theory, which is more fully treated by Cajal in a later chapter. Alice Rosenstein and Pollok deal respectively with the anatomy of the peripheral nerves and of the spinal cord and brain-stem, Gagel with the anatomy of the cerebellum, Spatz with that of the mid-brain, and Rose with the structure of the cerebral hemispheres. All these chapters are excellent, and as far as can be seen they are as complete as they could be in the pages allotted to them.

In the next chapter Rose describes the structure of the cerebral cortex, in more detail perhaps than is necessary in a volume of this character. It extends in fact to almost 200 pages, but it is liberally illustrated. Two useful chapters on the blood supply of the cerebral cortex and the distribution of neurologia in the nervous system by Freedom and Schroeder, are followed by one on the macroscopical and microscopical anatomy of the vegetative system by Greving. Before his death Cajal completed his section on the neurone theory and its significance in physiology and pathology. In the final chapter Boeke describes the mode and the principles of regeneration of nerve fibres.

Band VII. Erster Teil. *Humoralpathologie der Nervenkrankheiten.* Pp. 505, with 67 illustrations. Price RM. 82.

The whole of this volume, which has been written by F. Georgi and O. Fischer, is devoted to the pathology of the blood, urine and cerebrospinal fluid in nervous diseases. The first 200 pages deal with the blood and urine in various neurological conditions; the next 100 pages or so with the cerebrospinal fluid. In the latter section the presence in the fluid of ferments, hormones, immune bodies and other substances is fully discussed. The pathological changes, in the cerebrospinal fluid particularly, in all types of nervous diseases are fully described in the last chapter.

Each of these chapters contains an extraordinary wealth of facts and observations, many of which, though important, must be unknown to the ordinary neurologist; each is, in fact, a complete review of the subject with which it deals. There is probably no other single source in which so much information in these subjects can be found so scientifically collected together and so authoritatively correlated. A bibliography of nearly 100 pages and an adequate index make it possible to use this volume as a separate monograph.

Traité de Physiologie Normale et Pathologique: Physiologie Nerveuse. 2me Partie. E. G. ROGER et L. BINET. 1935. Paris: Masson et Cie. Pp. 1580, with 275 illustrations. Price fr. 250.

Volume 10, which appears in two parts, completes the system of Physiology which has been edited by Professors Roger and Binet. It is, as the preceding volume which we have already reviewed (vol. 56, p. 343), wholly devoted to the physiology and physiological pathology of the nervous system. Several of its chapters are of outstanding merit and interest, as that by Bremer on the cerebellum and that by Garcin on the functions of the cranial nerves and their disturbances. Probably nowhere are the functions of the vestibular apparatus more clearly and concisely presented than in the latter. There is also an excellent section on the sympathetic and parasympathetic systems, but recent work which has shown the important part played by chemical substances in the activity of these systems is scarcely referred to. Haguenau treats the cerebrospinal fluid on more or less conventional lines, and Logre, in his chapter on psychophysiology, deals almost exclusively with the mental symptoms due to mechanical or chemical damage, and those which develop on a constitutional basis. The chapters on the conduction and specific functions of the spinal cord and brain-stem are disappointing. Milian's excellent article on the physiology of the skin and its organs contains much valuable information, and H. Pieron's chapter on "le Toucher," that is sensations dependent on cutaneous and proprioceptive stimuli, attains the high level to be expected from its author. The physiology of the special senses is adequately presented in special sections. Froment writes on articulation and speech; the discussion of articulation and its disturbances is excellent. It can hardly be expected that the views of an author on speech and aphasia will receive general approbation, but the author presents his own attitude satisfactorily.

Huntington's Chorea. By JULIA BELL. The Treasury of Human Inheritance, Cambridge University Press, 1934. Vol. IV., "Nervous Diseases and Muscular Dystrophies," Part 1. Pp. 63, with 12 plates. Price 10s.

This study contains a brief account of the symptomatology of Huntington's chorea, a passing reference to its morbid anatomy and an analysis of the information which the author has collected as to its age and sex incidence, its duration and inheritance.

The onset of symptoms is commonest in the fourth decade of life, but the range of years over which the malady may make its first appearance is a wide one. The sex incidence is approximately equal and the duration averages some fourteen years. There is no direct relationship between the severity of the choreiform and of the mental disorder, in some cases the former and in others the latter is the predominant symptom.

The disease behaves as a dominant, being transmitted directly from parent to offspring. 151 pedigrees and histories are given. There is also a comprehensive bibliography of the clinical and pathological literature of the disease.

L'Abolition Isolée du Réflexe Pupillaire d'Adaptation à la Lumière. By A-M. H. LAGRANGE. Paris: Dion et Cie. 1935. Pp. 160. Price 40 francs.

The author undertakes a clinical study of the Argyll-Robertson phenomenon as observed in syphilitic and in non-syphilitic subjects, including in the latter category cases of the so-called "myotonic" pupil.

She confines her discussion to the loss of the light reaction and does not consider the possible significance of the other signs which together make up the syndrome in its complete form, namely, miosis, irregularity and inequality of pupils and atrophic changes in the iris. She refers to the work of Dupuy-Dutemps, who has emphasized the importance of considering all these components in any searching analysis of the syndrome, and who pointed out that the final state of the Argyll-Robertson pupil in long-standing cases of tabes is one of complete immobility. It may be doubted whether our knowledge of this complex and, so far, unexplained syndrome can be materially advanced until some generalization is found which will satisfactorily embrace all its components. The author completely evades this problem.

Ueber Myotonie. Klinische und erbpathologische Beiträge. Von H. BOETERS. Leipzig: Georg Thième. 1935. Pp. 82. Price RM. 5.60.

Boeters gives an extensive synopsis of published papers on myotonia congenita (Thomsen's disease) as well as on myotonia atrophica. The author himself examined twenty patients affected by myotonia and nearly all their relations living in Silesia. He publishes fourteen tables and twenty pedigrees. Like previous authors Boeters thinks the disease is transmitted by dominant heredity. Nisson, himself a member of the Thomsen family, has asserted that Thomsen's disease and myotonia atrophica were fundamentally different affections having nothing in common except myotonic disturbance, but Boeters, like Rosett and others, maintains that both affections are the same. He draws this conclusion, which has not been hitherto accepted by other authors, from having observed in the same families typical cases of both diseases. It would be of interest to know whether detailed examinations were performed (for example of lenses by slit-lamp) in order to make sure that cases considered to be Thomsen's disease were completely free from signs and symptoms considered pathognomic of myotonia atrophica.

Des Réflexes Conditionelles : Etudes de physiologie normale et pathologique. Par G. A. MARINESCO et A. KREINDLER. Paris: Librarie Félix Alcan. 1935. Pp. 168.

The authors give a general review of the observations and views associated with the name of Pavlov, and they attempt an application of these doctrines to a wide range of psychoneuroses and psychoses, and to the study of disorders of the speech function. This application, although it is illustrated by some clinical reports, is predominantly of a philosophic rather than of a clinical order.

The Autonomic Nervous System : Anatomy, Physiology and Surgical Treatment. By J. C. WHITE. London: Henry Kimpton. 1935. Pp. 386. Price 30s.

The chief interest of this book lies in its detailed account of the various surgical procedures now practised upon the sympathetic system. These are described from the technical and the clinical aspects and the author affords a comprehensive review of the present state of the surgery of the sympathetic system, and of the results so far obtained.

Although theoretical arguments are not lacking to rationalize the ever-increasing number of such interventions, and the steadily growing range of maladies and symptoms for which they are carried out, it appears that in some instances they are in the nature of "shots in the dark," undertaken hopefully because no other adequate method of relief or cure is available.

Even where the theoretical basis of operation appears sound the results are sometimes profoundly discouraging. The treatment of epilepsy provides a case in point. It has been observed that stimulation of the cervical sympathetic decreases the capillary bed within the brain, while sympathectomy increases it by some 50 per cent. It has also been reported that when the brain is exposed the onset of an epileptic fit is heralded by a local spasm of cortical arteries. It has been argued, therefore, that bilateral cervicothoracic ganglionectomy which effects complete sympathetic denervation of the brain should prevent the occurrence of epileptic fits. White records seventeen cases so treated. In two only of these is it possible to see any remarkable sequence of the operation. The patients were children of the ages of 7 and 14 respectively, and their liability to fits was in each case of short duration. Both have since remained (for three years) free from all fits. But it is doubtful whether anyone familiar with the natural history of the malady, and aware that sometimes in childhood epileptic fits cease spontaneously for a period of years, would venture to find these results as encouraging as does the author, and the reader is left with the impression that greater discrimination in the use of sympathetic surgery might in the end sooner reveal its scope of usefulness, and avert many fruitless operations upon the sick.

Individual Psychology: Medical Pamphlets: Nos. 11A, 12, 13, 14. London: C. W. Daniel. 1934-35. Pp. 55. Price 2s. 6d. each.

This little collection of papers delivered by Alfred Adler and his followers in England is characteristic of what individual psychology has now become, a useful, limited, intellectually unambitious way of dealing with neurotic problems. The outlook of some of the writers is simple to the point of naïveté; others have a background of philosophic interest, here best propounded by Dr. Leonhard Seif, a typically Adlerian approach to "life philosophy."

Mental Health: Its Principles and Practice. By F. E. HOWARD and F. L. PATRY. New York: Harper and Bros. 1935. Pp. 551. Price 15s.

Mental hygiene is necessarily propagandist, with the result that many of the books dealing with it are vague and enthusiastic, when the reader would prefer them to be concrete. This book, although wordy, is more satisfying to the medical reader. The teaching of Adolf Meyer is presented in it coherently so that the psychiatric part offers an easy but sound introduction to this difficult subject. In the first third of the book sexual and other psychological problems are elucidated from the standpoint of mental hygiene; the remainder is taken up with "ergosiology," or objective psycho-biology, and the methods of recognizing and dealing with deviations from mental health, especially those which occur in children. Educational problems are dealt with more fully than is usual in such works.

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